CLINICAL PROTOCOL HGS1006-C1121
Protocol Amendment: 07
EudraCT Number: 2011-004570-28
Date: 24 January 2019

TITLE OF STUDY:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Belimumab plus Standard of Care versus Placebo plus Standard of Care in Adult Subjects with Active Lupus Nephritis

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Revision Chronology for HGS1006-C1121 (BEL114054)

	Date	Document*
Global	19 October 2011	Original
Global	27 January 2012	Amendment No 01
Global	08 March 2012	Amendment No 02
Local	16 August 2012	Amendment 02 for Thailand
Global 2013N179093_00	11 February 2014	Amendment No 03
Local 2014N205397_00	29 August 2014	Amendment 04 for China
Global 2013N179093_01	16 March 2015	Amendment No 05
Local 2013N179093_02	17 March 2015	Amendment No 05 for France
Local 2013N179093_03	13 July 2016	Amendment No 05/France-2
Global 2013N179093_04	25 April 2017	Amendment No 06
Local 2013N179093_05	26 April 2017	Amendment No 06/France-2
Global 2013N179093_06	24 January 2019	Amendment No 07

*A Summary of Modifications document which provides a detailed list of changes for the amendment/addendum is available upon request.

INVESTIGATOR AGREEMENT

I will provide copies of the protocol, any subsequent amendments and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational study agent and the study protocol. I agree to conduct this clinical trial according to the protocol described herein, except when mutually agreed to in writing with the sponsor. I also agree to conduct this study in compliance with Good Clinical Practice (GCP) standards as defined by the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice, all applicable national, state, and local regulations, as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) and any other institutional requirements.

Principal Investigator:

Signature *Date (dd mmm yy)*

Name (please type or print)

Institution

Address

STUDY SYNOPSIS

Study Number: HGS1006-C1121

Title of the Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Belimumab plus Standard of Care versus Placebo plus Standard of Care in Adult Subjects with Active Lupus Nephritis

Clinical Development Phase: 3

Objectives:

- To evaluate the efficacy of belimumab in combination with standard of care in adult subjects with lupus nephritis Class III, IV, or V using the 2003 International Society for Nephrology (ISN)/Renal Pathology Society (RPS) criteria.
- To assess the safety and tolerability of belimumab plus standard of care versus placebo plus standard of care in adult subjects with lupus nephritis Class III, IV, or V using the 2003 ISN/RPS criteria.

Diagnosis & Inclusion Criteria: Subjects enrolled in the study must meet the following inclusion criteria:

1. Males or females at least 18 years of age.
2. Have a clinical diagnosis of systemic lupus erythematosus (SLE) according to the American College of Rheumatology (ACR) criteria (Appendix 1).
3. Have active, biopsy-proven proliferative lupus nephritis Class III or IV [excluding Class III(C), IV-S(C), and IV-G(C)] either with or without the presence of Class V, or pure Class V membranous using the 2003 ISN/RPS criteria (Appendix 2); the biopsy must be performed in the 6 months prior to the screening visit or during the screening period. The local biopsy report will be used to confirm subject eligibility. A tissue sample from the renal biopsy used to qualify the subject for randomization needs to be sent to a central reading center after Day 0 (baseline).
4. Have unequivocally positive anti-nuclear antibody (ANA) test results defined as an ANA titer ≥ 1:80 (based on Hep-2 immunofluorescence assay or equivalence by enzyme immunoassay assay), and/or a positive anti-dsDNA (≥ 30 IU/mL based on ELISA assay) serum antibody test at the screening visit based on the study's central laboratory results.
5. Have documentation of active renal disease at screening requiring induction therapy with high dose corticosteroids (HDCS) with either intravenous (IV) cyclophosphamide (CYC) or mycophenolate mofetil (MMF) or other oral forms of mycophenolate. The following factors will be used to define active renal disease at screening:
    - Urinary protein:creatinine ratio of ≥ 1.0 AND
        - Active urinary sediment as defined by at least 1 of the following (in absence of menses and genitourinary tract infection).

- > 5 red blood cell (RBC)/high power field (hpf) or above the laboratory reference range.
- > 5 white blood cell (WBC)/hpf or above the laboratory reference range.
- Presence of cellular casts (RBC or WBC).

– Subjects without active urinary sediment are eligible if they meet at least 1 of the following criteria:

– Have a confirmatory biopsy performed within 3 months prior to the screening visit or during the screening period meeting the criteria outlined in Inclusion Criterion 3.
– Have proteinuria ≥ 3.5 grams/day (or urinary protein:creatinine ratio≥ 3.5).

6. Have active renal disease defined as above which requires induction therapy with high dose corticosteroids (HDCS) with either intravenous (IV) cyclophosphamide (CYC) or mycophenolate mofetil (MMF) or other oral forms of mycophenolate:

   Induction therapy may begin before Screening but should be initiated within 60 days prior to or on Day 0 (baseline). Initiation of induction is when both HDCS and either MMF or CYC have been started.

   The study recommended doses for induction therapy are as follows, adjustments may be made for tolerability issues (refer to Section 5.5.1 Standard of Care Medication for details):

   - MMF 1-3g/day orally or Mycophenolate sodium 720 - 2160 mg/day orally
   - corticosteroids: 0-3 IV pulses of methylprednisolone 500 -1000 mg/pulse followed by oral prednisone 0.5-1.0 mg/kg/day with total daily dose up to 60 mg/day (or equivalence)
   - CYC 500 mg by IV infusion every 2 weeks (± 3 days) for 6 infusions

   Subjects who have been on MMF for SLE including lupus renal disease may be eligible if they have received, or will receive, the following induction therapy within 60 days prior to or on Day 0:

   - initiation of HDCS with MMF dose increase to reach the target dose for induction in the subject (if the subject did not previously fail MMF induction based on the investigator's opinion), OR
   - initiation of HDCS with discontinuation of MMF and initiation of CYC.

   Note: It is recommended that subject eligibility should be discussed with the Medical Monitor if a subject initiated but did not complete an induction therapy within 6 months prior to the initiation of current induction therapy for the study.

7. A female subject is eligible to enter the study if she is:

   - Not pregnant or nursing;
   - Of non-childbearing potential (ie, women who had a hysterectomy, are postmenopausal which is defined as 1 year without menses, have both ovaries

surgically removed, or have current documented tubal ligation or any other permanent female sterilization procedure); or

- Of childbearing potential (ie, women with functional ovaries and no documented impairment of oviductal or uterine function that would cause sterility). This category includes women with oligomenorrhoea [even severe], women who are perimenopausal, or have just begun to menstruate. These women must have a negative serum pregnancy test at screening, and agree to 1 of the following:
  - Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent; or
  - Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during study, and for 16 weeks after the last dose of study agent:
    - Implants of levonorgestrel or etonogestrel;
    - Ethinyl estradiol/Etonogestrel vaginal ring;
    - Injectable progesterone;
    - Any intrauterine device (IUD) with a documented failure rate of less than 1% per year;
    - Oral contraceptives (either combined or progesterone only);
    - Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) with spermidical foam/gel/film/cream/suppository;
    - Transdermal contraceptive patch;
    - Male partner sterilisation with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

    Note: 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.

8. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study protocol procedures (including required study visits).

Exclusion Criteria: Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Subjects who have previously failed both CYC and MMF (or other forms of mycophenolate) induction therapies based on the investigator's opinion. If a subject has failed only 1 of the 2 therapies for induction, they may be eligible for study inclusion if the other induction therapy is initiated within 60 days prior to or on Day 0 (ie, a subject who failed MMF is eligible if newly initiating induction therapy with CYC or a subject who failed CYC is eligible if newly initiating induction therapy with MMF).
2. Subjects who received an induction therapy with CYC within 3 months prior to the planned initiation of the current induction for the study.
3. Subjects who receive CYC whose pre-induction leukocyte count is Grade 3 or 4 based on the Adverse Event Severity Grading Tables (Appendix 7).
4. Known hypersensitivity or contraindication to any drug products or any component of these drug products they plan to receive (eg, CYC, MMF, azathioprine (AZA), corticosteroids).
5. Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.
6. Have received treatment with belimumab within 364 days of baseline (Day 0).
7. Received any of the following within 364 days of baseline (Day 0):
   - Nitrogen mustard
   - Chlorambucil
   - Vincristine
   - Procarbazine
   - Etoposide
   - Abatacept
   - Treatment with any B cell targeted therapy (eg, rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI-Fc, or LY2127399 [anti-BAFF])
   - A biologic investigational agent (eg, abetimus sodium, anti-CD40L antibody [BG9588/ IDEC-131]). Investigational agent applies to any drug not approved for sale in the country in which it is being used.
   - Treatment with interleukin-6 targeted therapy (e.g., tocilizumab, sirukumab).
8. Received any of the following within 90 days of baseline (Day 0):
   - Anti-TNF therapy (eg, adalimumab, etanercept, infliximab, certolizumab, golimumab pegol)
   - Interleukin-1 receptor antagonist (anakinra).
   - Intravenous immunoglobulin (IVIG).
   - Plasmapheresis.
9. Received a non-biological investigational agent within 60 days of baseline (Day 0).

10. Received a live vaccine within 30 days of baseline (Day 0).
11. 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 baseline (Day 0).
12. Have a history of a major organ transplant (eg, heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant or are due to receive transplantation.
13. Subjects who have been on dialysis within 364 days of baseline (Day 0).
14. An estimated glomerular filtration rate < 30 mL/min/1.73 m^2 at the screening visit (using the simplified Modification of Diet in Renal Disease [MDRD] equation).
15. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to SLE (ie, cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, 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 a planned surgical procedure or a history of any other medical disease (eg, cardiopulmonary), laboratory abnormality, or condition (eg, poor venous access) that, in the opinion of the principal investigator, makes the subject unsuitable for the study.
17. Have a history of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix.
18. Have acute or chronic infection requiring management, as follows:
    - Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster, or atypical mycobacteria).
    - Hospitalization for treatment of infection within 60 days of baseline (Day 0).
    - Have had infection requiring treatment with parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of baseline (Day 0).
19. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to baseline (Day 0).
20. Have a historically positive test or test positive at screening for HIV antibody.
21. Hepatitis B: Serologic evidence of Hepatitis B (HB) infection based on the results of testing for HBsAg, anti-HBc and anti-HBs as follows:
    - Patients positive for HBsAg are excluded.
    - Patients negative for HBsAg but positive for Anti-HBc, regardless of Anti-HBs antibody status, will require clarification of their status by testing for HBV DNA
    - o if HBV DNA positive, patients will be excluded from participation
    - o if HBV DNA negative, patients will be eligible to enrol.
    - NOTE: For those subjects randomised, additional ongoing assessment during the study is required (see Section 6.7.5).

22. Hepatitis C: Positive test for Hepatitis C antibody confirmed on a subsequent blood sample by RNA-PCR assay. Subjects who are positive for Hepatitis C antibody and negative when the Hepatitis C RNA-PCR assay is performed on a subsequent sample will be eligible to participate. Subjects who are positive for Hepatitis C antibody and have a positive result for the HCV when the Hepatitis C RNA-PCR assay is performed on the subsequent sample will not be eligible to participate. Subjects in China with positive test for Hepatitis C antibody will be excluded without confirmatory Hepatitis C RNA-PCR testing.
23. Have an IgA deficiency (IgA level < 10 mg/dL).
24. Have a Grade 3 or greater laboratory abnormality (including serum IgG level) based on the Adverse Event Severity Grading Tables (Appendix 7) except for the following that are allowed:
    - Urinalysis (eg, proteinuria)
    - Hematuria
    - Pyuria
    - Casts
    - Hypoalbuminemia due to lupus nephritis
    - Stable Grade 3 prothrombin time (PT) secondary to warfarin treatment.
    - Stable Grade 3 partial thromboplastin time (PTT) due to lupus anticoagulant and not related to liver disease or anti-coagulant therapy.
    - Stable Grade 3 gamma glutamyl transferase (GGT) elevation due to lupus hepatitis, and not related to alcoholic liver disease, uncontrolled diabetes or viral hepatitis. If present, any abnormalities in the ALT and/or AST must be ≤ Grade 2.
    - Stable Grade 3 reduction in hemoglobin levels due to SLE
    - Stable Grade 3 neutropenia or stable Grade 3 white blood cell count [with the exception of subjects receiving CYC who will be excluded if WBC is Grade 3 or 4 per Exclusion Criterion 3]. Note that WBC count should be obtained immediately prior to starting induction therapy. If immediate pre-induction WBC is not available, a WBC count obtained within 28 days prior to induction may be used.
    - Hyperuricemia or blood urea nitrogen (BUN) elevation due to lupus nephritis or SLE.
25. Subjects who 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 Columbia- Suicide Severity Rating Scale (C-SSRS) (Appendix 8) in the last 2 months or who, in the investigator's opinion, pose a significant suicide risk.

Study Design and Schedule:

This is a Phase 3, multi-centre, multi-national, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of IV belimumab 10 mg/kg plus

standard of care compared to placebo plus standard of care in adult subjects with active lupus nephritis.

Subjects who meet the eligibility criteria during screening will be randomized to 1 of 2 treatment groups in a 1:1 ratio: 10 mg/kg belimumab plus standard of care or placebo plus standard of care. The randomization of all eligible subjects will be stratified by their induction regimen (high dose cortiocsteroids [HDCS] plus CYC vs HDCS plus MMF) and race (black race vs other). Subjects will be dosed with study agent on Days 0 (baseline), 14, 28 and then every 28 days thereafter through 100 weeks with a final evaluation for the double-blind treatment period at 104 weeks. At least 400 and up to approximately 464 lupus nephritis subjects will be randomized with a target of at least 200 and up to approximately 232 subjects in each treatment group (belimumab or placebo). All subjects will receive background therapy consisting of one of the following standard of care regimens:

- High Dose Corticosteroids (HDCS) + Cyclophosphamide (CYC) for induction therapy followed by Azathioprine (AZA) for maintenance therapy

  OR

- HDCS + Mycophenolate Mofetil (MMF) for induction therapy followed by MMF for maintenance therapy

The standard of care medications are described in Section 5.5.1.

All subjects should start the above induction therapy within 60 days prior to or on Day 0 (baseline visit). This will allow subjects to be screened and potentially enrolled and will not be excluded on the basis of necessary acute management. The primary efficacy endpoint of a renal response will be determined by changes in proteinuria and renal function at Week 104. For the renal function assessments at all study visits, the glomerular filtration rate (GFR) will be estimated using the simplified MDRD formula; proteinuria will be evaluated using the urinary protein: urinary creatinine ratio. In addition, at baseline, Week 24, 48, 52, 76, 100 and 104, GFR will be calculated based on creatinine clearance determined from the mean creatinine value of 2 contiguous 24 hour urine collections and 2 serum creatinine measurements. The first serum creatinine will be collected at an initial visit which will take place within 3 days prior to or on the day of the scheduled visit. At the initial visit, subjects will be provided with the materials for collecting the two 24 hour urine collections beginning the next morning following their initial clinic visit. On the third day following the initial visit, subjects will return to the clinic for the second serum creatinine sample.

Urine collection may be postponed up to 14 days at the investigators discretion if menstrual bleeding or a genitourinary tract infection is present at any time during the 24 hour urine collection.

The primary endpoint will be measured using the Primary Efficacy Renal Response (PERR) based on study defined criteria (see Section 8.5). Week 104 PERR will be

defined by a response at Week 100 that is confirmed by a repeat measurement at Week 104.

All subjects who discontinue treatment with study agent during the double-blind period (for reasons other than withdrawal of consent) should return for all scheduled visits through Week 104.

In the event that a subject withdraws consent from the study, an attempt should be made to obtain consent to collect follow-up safety data (at an exit visit approximately 4 weeks after the last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent) and to obtain survival status at Week 104. Any subject that withdraws consent for use and disclosure of research-related health information will be considered withdrawn from the study and will not be followed for mortality.

Subjects who receive treatment with study agent through Week 100 and complete Week 104 assessments in the double-blind period may enter into a 6-month open-label extension. The Week 104 visit of the double-blind period will serve as the Day 0 visit for subjects entering the open-label extension. In the open-label extension, all subjects will receive 10 mg/kg belimumab every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the last dose). The first dose on the open-label extension will be given at the Week 104 visit of the double-blind period following the completion of all Week 104 assessments. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety as per the study calendar (see Table 6-3). Subjects who complete the 104-week double-blind period, but do not enter the open-label extension will be required to return for an additional follow up visit 8 weeks after the last dose of study agent. All subjects who enter the open-label extension period and withdraw early will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent.

At the end of the 6-month open-label extension period, subjects who wish to continue treatment may do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may continue to receive belimumab under a separate continuation protocol if permissible according to local regulations. A separate informed consent will need to be provided for the continuation protocol. The 8-week follow-up visit is not required for subjects entering the continuation protocol.

Efficacy Endpoints and Analysis:

The primary efficacy endpoint is Primary Efficacy Renal Response (PERR) at Week 104, as follows:

- Responder: Defined by a response at Week 100 confirmed by a repeat measurement at Week 104, as follows:

  Estimated glomerular filtration rate (GFR) is no more than 20% below the pre-flare value or $\geq$ 60 mL/min/1.73m^2

AND

Urinary protein:creatinine ratio ≤ 0.7

AND

No receipt of prohibited (rescue) therapy resulting in treatment failure (see Section 5.5 and Section 5.6).

- Non-responder: Not meeting criteria for the PERR.

Major Secondary Endpoints:

- Complete Renal Response (CRR) at Week 104 (see definition under Ordinal Renal Response).
- PERR at Week 52.
- Time to Death or Renal-related Event defined as any of the following: i) end stage renal disease (ESRD), ii) doubling of serum creatinine, iii) renal worsening as evidenced by increased proteinuria and/or impaired renal function, or iv) renal disease-related treatment failure.
- Ordinal Renal Response (ORR; complete, partial or no response) at Week 104 defined as follows:
  - Complete Renal Response (CRR):

    Estimated glomerular filtration rate (GFR) is no more than 10% below the pre-flare value or within normal range

    AND

    Urinary protein:creatinine ratio < 0.5

    AND

    No receipt of prohibited (rescue) therapy resulting in treatment failure (see Section 5.5 and Section 5.6).

  - Partial Renal Response (PRR):

    Estimated GFR no more than 10% below the baseline value or within normal range

    AND

    ≥ 50% decrease in the urine protein:creatinine ratio with one of the following:
    - a urine protein:creatinine ratio of < 1.0, if the baseline ratio was ≤ 3.0
      OR
    - a urine protein:creatinine ratio of < 3.0, if the baseline ratio was > 3.0

AND

– No receipt of prohibited (rescue) therapy resulting in treatment failure (see Section 5.5 and Section 5.6).

- No Renal Response (NRR):

  Not meeting criteria for either CRR or PRR.

Sample Size Calculation:

The sample size was calculated using the ORR as the primary endpoint and assuming the primary endpoint proportions of complete, partial, and no renal response will be 25%, 25%, and 50% respectively, for subjects on placebo plus standard of care (Appel et al, 2009; Sinclair, 2007; Dooley et al, 2011) and 32.5%, 32.5% and 35%, respectively, for subjects on belimumab plus standard of care. Using these assumptions, simulations were performed using Van Elteren methods at the 5% significance level and a 1:1 randomization allocation ratio, a target sample size of N=464 subjects (232 per arm) is required to achieve at least 85% power to detect a treatment difference for the primary endpoint.

For the new primary endpoint, PERR (Responder vs. Non-Responder), and the final sample size of N=448, there is 80% power to detect a 13.6% treatment difference and a minimum detectable difference of 9.7% for response rates spanning the 50% mark of the binomial distribution (40% vs. 53.6%), the area of maximum variance.

Analysis of Primary Efficacy Endpoint:

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

Analysis of Major Secondary Efficacy Endpoints:

Time to death or renal-related event will be compared between belimumab vs. placebo using a Cox proportional hazards model controlling for induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline proteinuria, and baseline eGFR.

CRR at Week 104 and PERR at Week 52 will be compared between belimumab and placebo using logistic regression controlling for induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline proteinuria, and baseline eGFR.

Analysis of ORR (complete, partial or no response) at Week 104 will be compared between belimumab vs. placebo using rank analysis of covariance (ANCOVA) controlling for induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline proteinuria, and baseline eGFR.

For the analysis of the primary and the major secondary efficacy endpoints, a step-down sequential testing procedure will be used to control the overall type 1 error (Section 8.1).

Other efficacy endpoints are described in Section 8.5.4.

Safety Endpoints and Analysis:

Descriptive statistics will be used to summarize adverse events (AEs), changes in laboratory parameters, and immunogenicity. The frequency and incidence of laboratory abnormalities will be tabulated by treatment group. The frequency and incidence of AEs will be tabulated by MedDRA system organ class (SOC) and preferred term and compared between placebo and the belimumab treatment group.

An Independent Data Monitoring Committee (IDMC) will review unblinded safety data on an ongoing basis until data through Week 104 of the double-blind treatment period are locked and analyzed (after which time monitoring may be assumed by an internal GSK/HGS committee). The IDMC will include physicians with expertise in infectious disease, rheumatology or nephrology and a statistician, none of whom are affiliated with the sponsor. The first review will occur 6 months after the first subject is randomized or after the first 20 subjects are randomized and have completed a Week 8 visit, whichever is sooner. Thereafter, the IDMC will review the data approximately every 6 months. At all times the sites and sponsor will remain blinded to treatment allocation. Events to be monitored during the safety review will include at a minimum all serious adverse events (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 Week 104 and open-label extension portions of the study. Investigators (and IRBs/IECs, as appropriate,) will be notified of the outcome of each IDMC meeting.

Pharmacokinetics Endpoints and Analysis:

Blood samples will be collected during the study and analyzed to determine serum belimumab concentrations. Serum belimumab concentration data will be used in a population PK analysis, which will be reported separately.

Immunogenicity:

Serum samples for anti-belimumab antibody measurements will be obtained from all randomized subjects before administration of study agent at the baseline visit (Day 0), Week 8, Week 24, Week 52, Week 76 and Week 104. During the 6 month open-label extension, samples will be obtained at Week 24. Additionally, a sample will be collected at the 8-week follow-up visit.

Biological Markers and Autoantibodies:

The following biomarkers will be measured at baseline (Day 0) and at selected timepoints thereafter:

- Autoantibodies: ANA, anti-dsDNA, aCL (IgG, IgM, IgA isotypes), anti-Sm, and anti-C1q
- Serum immunoglobulin isotypes: IgA, IgG, IgM
- Serum complement (C3,C4)
- BLyS protein (baseline only)

In geographies where feasible, the following biological markers will be measured (using FACS analysis) at baseline (Day 0) and at multiple time points thereafter:

- Peripheral B lymphocytes:
  - $CD20^{+}$, $CD20^{+}/27^{+}$ memory, $CD20^{+}/27^{-}$ naïve, $CD20^{+}/69^{+}$ activated, $CD20^{+}/138^{+}$ plasmacytoid, $CD19^{+}/27^{BRIGHT}/38^{BRIGHT}$ SLE subset, $CD19^{+}/CD24^{HIGH}/CD38^{HIGH}$ regulatory B cells, and $CD20^{-}/138^{+}$ plasma cells.

An exploratory analysis of urinary biomarkers related to lupus nephritis may be performed at baseline (pre-dose) and at selected timepoints thereafter. Data collection and analysis will be performed independently of the main study and will form the basis of a separate report. The biomarkers include, but are not limited to, MCP-1, hepcidin, NGAL, LFABP, Angiogenin, Angiopoietin 2, Angiostatin, IL-6r, Osteopontin, PAI-1, PF4, RAGE, RANK, Sgp130, Siglec 5, Siglec 9, Tgf-beta1, TIM1, TIMP-2, TLSP, TNFR-II, Trem1, VCAM-1, Vegf-C, and VEGF-R3.

Study Calendar:

See Table 6-1, Table 6-2, and Table 6-3 for a calendar of study visits and assessments.

Study Schematic: See Figure 1-1.

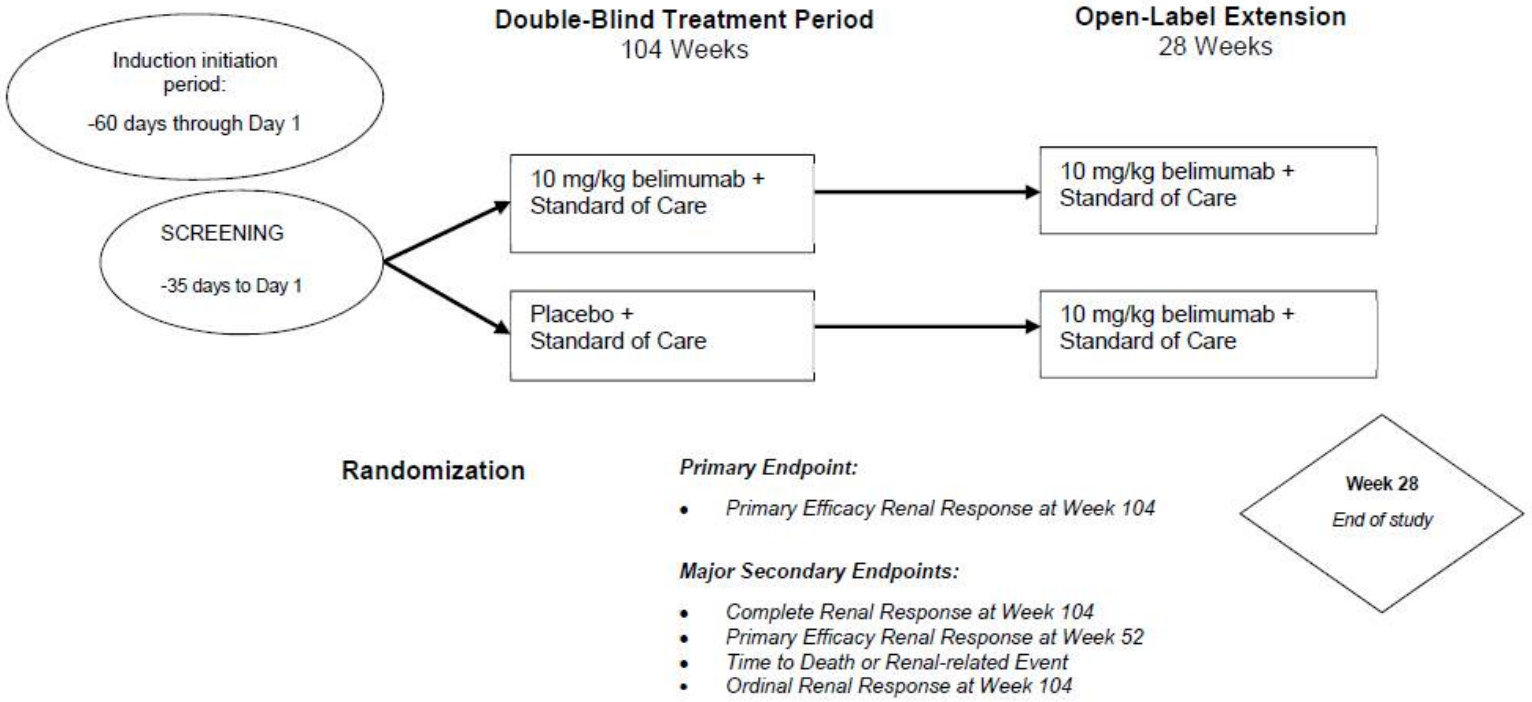

Figure 1-1 Study schematic

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aCL	anticardiolipin
ACE	angiotensin converting enzyme
ACR	American College of Rheumatology
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ANCOVA	analysis of covariance
ARB	angiotensin receptor antagonists/blockers
anti-dsDNA	anti-double-stranded DNA
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antigen antibody
anti-Sm	anti-Smith antibody
anti-TNF	anti-tumor necrosis factor
AST	aspartate aminotransferase
AUC	area under the serum drug concentration-time curve
AUCi	area under the curve for an individual subject
AZA	azathioprine
bid	twice a day
BILAG	British Isles Lupus Assessment Group of SLE Clinics
BLyS	B lymphocyte Stimulator
BR3	BLyS-receptor fusion protein
BUN	blood urea nitrogen
ºC	degrees Celsius
CD	compact disc
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CRR	complete renal response
C-SSRS	Columbia-Suicide Severity Rating Scale
CYC	cyclophosphamide
CVA	cerebrovascular accident
dL	deciliter
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
dsDNA	double-stranded DNA
eCRF	electronic case report form
ECL	electrochemiluminescence
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorobent assay
ESRD	end stage renal disease
EU	European Union
FACS	florescence activated cell sorting
FDA	United States Food and Drug Administration

g	gram
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GSK	GlaxoSmithKline Pharmaceuticals
HB	Hepatitis B
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBc	Hepatitis B core antigen
HCV	Hepatitis C virus
HDCS	high dose corticosteroids
Hep-2	human epithelial cell line 2
HGS	Human Genome Sciences, Inc.
HIV	human immunodeficiency virus
hpf	high power field
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IM	intramuscular
IRB	Institutional Review Board
ISN	International Society for Nephrology
ITT	intention to treat
IU	international unit
IUD	intrauterine device
IV	intravenous
IVIG	intravenous immunoglobulin
IWRS	Interactive Web Response System
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	kilogram
LDH	lactic dehydrogenase
LOCF	last observation carried forward
MDD	major depressive disorder
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MTX	methotrexate
µg	microgram
mg	milligram
mL	milliliter
mmHG	millimeters of mercury
NMSC	non-melanoma skin cancer
NR	no response
NSAIDs	non-steroidal anti-inflammatory drugs
NWHIC	National Women's Health Information Center

OMHRC	Office of Minority Health Resource Center
ORR	ordinal renal response
PERR	primary efficacy renal response
PGA	Physician's Global Disease Assessment
PGx	pharmacogenetics
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PRR	partial renal response
PSE	protocol-specified event
PSRHQ	possible suicidality-related history questionnaire
PSRQ	possible suicidality related questionnaire
PT	prothrombin time
PTT	partial thromboplastin time
PY	patient-years
RA	rheumatoid arthritis
RBC	red blood cell
RPS	Renal Pathology Society
RRGFR60	renal response using 60 mL/min/1.73m^2 eGFR cut off
RRUS	renal response including urinary sediment component
SAE	serious adverse event
SAS	statistical analysis system
SC	subcutaneous
SELENA	Safety of Estrogen in Lupus National Assessment trial
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SOC	System Organ Class
SRI	systemic lupus erythematosus responder index
SWFI	sterile water for injection
TACI-Fc	transmembrane activator attached to Fc portion of an immunoglobulin
tid	three times daily
TNF	tumor necrosis factor
ULN	upper limits of normal
uPCR	urine protein-creatinine ratio
US	United States of America
USAN/INN	United States adopted name/international nonproprietary name
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND

1.1. Disease Background Relevant to Clinical Study

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by autoantibody production and abnormal B lymphocyte function (Pisetsky, 2001). The etiology of SLE is unknown, although genetics, sex hormones, and environmental conditions are thought to play a role (Kotzin, 1996; Pisetsky, 1998; Sobel et al, 1999). This disease is more common in women (~90% of patients) than men (NWHIC, 2003) and more prevalent in African-Americans than Caucasians (OMHRC, 2001; NWHIC, 2003). In the United States (US) the reported prevalence is 100,000 to 500,000 patients with some estimates of 1 million as the incidence increased 2-3 fold between 1950 and 1979. In the European Union (EU), prevalence rates have been reported ranging from 25 to 39 cases per 100,000 persons (Jiménez et al, 2003). In community-based studies among Asians, the prevalence (per 100,000) of SLE ranged from 3.2 to 70.4 (Thumboo and Wee, 2006). The disease onset is generally between the ages of 20 and 40. Patients with SLE have about a 3-fold greater risk of mortality than the general population. Approximately 70% of SLE patients survive 20 years from time of diagnosis (Houssiau et al, 2004).

SLE can lead to arthritis, kidney failure, heart and lung inflammation, central nervous system (CNS) changes, vasculitis, severe skin rash, and blood dyscrasias such as anemia, leukopenia, and thrombocytopenia. The manifestations of SLE vary from patient to patient and it may take many years to render the proper diagnosis. The American College of Rheumatology (ACR) criteria that define a diagnosis of this heterogeneous disease require 4 of 11 criteria that include SLE-associated signs or symptoms, lab abnormalities, and the presence of specific anti-nuclear autoantibodies (Tan et al, 1982).

Approximately 35% of all adult patients with SLE develop clinically significant lupus nephritis and despite improvements in both diagnosis and treatment over the last few decades it remains an indicator of poor prognosis (Gordon et al, 2009; Waldman and Appel, 2006). Manifestations of lupus nephritis include proteinuria, elevations in serum creatinine, and the presence of urinary sediment. Alongside these clinical manifestations, morphological changes can be observed in renal biopsy specimens. In 1975 the World Health Organization (WHO) proposed a classification system for renal biopsies in SLE which was continually revised by them up until 1995. In 2004 updated criteria jointly developed by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) were published (Weening et al, 2004). Within the 5 overall classes, Classes I and II reflect disease restricted to mesangial abnormalities. Classes III and IV represent either focal (< 50% glomeruli involved - Class III) or diffuse (≥ 50% glomeruli involved - Class IV) segmental or global glomerulonephritis. Class V represents membranous disease with Class VI representing advanced sclerosis. Classes I and II are rarely accompanied by clinical manifestations and there is no activity in Class VI only damage, so therapy has traditionally focused on Classes III-V.

Belimumab (BENLYSTA™) administered intravenously (IV) is approved in the US, Canada, and EU for the treatment of adult patients with active autoantibody-positive SLE

who are receiving standard therapy; patients with severe active lupus nephritis and severe active CNS lupus were excluded, as were patients receiving other biologics and IV cyclophosphamide (refer to specific country labeling for additional information regarding the approved indication). Approval of IV belimumab for SLE is being sought in other regions of the world.

1.2. Belimumab

1.2.1. Mechanism of Action

Belimumab (also known as LymphoStat-B™; BENLYSTA™) is a B lymphocyte stimulator (BLyS)-specific inhibitor that blocks the binding of soluble BLyS, a B cell survival factor, to its receptors on B cells. Belimumab does not bind B cells directly, but by binding BLyS, belimumab inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

Nonclinical pharmacology, pharmacokinetic (PK), and toxicology data generated with belimumab are provided in the Investigator's Brochure (IB).

1.2.2. Clinical Experience with Belimumab

Belimumab administered as an IV infusion has been studied in SLE patients in 1 Phase 1 trial (LBSL01), 1 Phase 2 randomized, double-blind, placebo-controlled trial (LBSL02), and 2 Phase 3 randomized, double-blind, placebo-controlled trials [BLISS 52 (HGS1006-C1057) and BLISS 76 (HGS1006-C1056)], and in rheumatoid arthritis (RA) patients in a Phase 2 double-blind, placebo-controlled trial (LBRA01).

Phase 3 studies of belimumab in SLE were completed in 2009 and 2010 and formed the basis of the approval of IV belimumab in the US, Canada, and EU. The Phase 3 trials included 1,684 subjects where belimumab 10 mg/kg plus standard therapy demonstrated superiority over placebo plus standard therapy in reduction in disease activity as measured by the SLE responder index (SRI) with an acceptable safety profile. The primary safety population supporting approval also included data from a Phase 2 study in 449 subjects with SLE. Evidence of benefit in other clinical measures such as reductions in disease activity as measured by SELENA SLEDAI, severe flare, and reduced steroid use was also observed. Treatment with belimumab plus standard of care was generally well tolerated, with rates of adverse events (AEs), severe AEs, serious AEs, AEs leading to discontinuation, and serious/severe infections generally comparable to the rates observed in the placebo plus standard of care group. Mortality rates in the controlled clinical trials were low, although numerically higher in the belimumab groups: 0.4% and 0.8% in the placebo and belimumab groups, respectively. Causes of death were as expected in an SLE population with active disease receiving a wide range of standard therapies, such as steroids and immunosuppressants, and included infection, cardiovascular disease, and suicide. Serious infections were observed in 5.2% and 6.0% of subjects receiving placebo and belimumab, respectively. The rate of malignancy (excluding non-melanoma skin cancer) was the same between the placebo and belimumab groups at 0.4%; however, as with other immunomodulating agents, the

mechanism of action of belimumab could increase the risk for the development of malignancies. Hypersensitivity and infusion reactions were observed. Anaphylaxis was also observed, though rare (< 1%). Depression-related events, common in patients with SLE, were observed more frequently with belimumab than with placebo; it is unknown if belimumab treatment is associated with an increased risk for these events. The most commonly-reported adverse reactions, occurring in ≥ 5% of patients in clinical trials, were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis.

Experience from open-label, long-term continuation trials of belimumab in SLE subjects suggests that prolonged treatment with belimumab remains generally well tolerated, with no apparent increase in the incidence rate of AEs or serious adverse events (SAEs) over time, including important events such as infections and malignancies. The prevalence rate of AEs and SAEs has also remained relatively stable over time. Long term belimumab treatment through 6 years appears to provide sustained improvement in SLE disease activity.

Results of the clinical trials of belimumab administered IV are described in further detail in the Investigator's Brochure.

1.3. Rationale for the Study

Current standard of care treatment for lupus nephritis consists of corticosteroids and immunosuppressants. Several studies have now been conducted in lupus nephritis; however at this time no therapies have been approved for lupus nephritis. In the Euro-lupus trial, a low dose IV cyclophosphamide (CYC) regimen achieved similar clinical results with respect to treatment failures, renal remission and renal flares when compared to a high dose IV CYC regimen (Houssiau et al, 2002). A recent systematic review of recent trials in lupus nephritis concluded that mycophenolate mofetil (MMF) is as effective as CYC in inducing disease remission (Touma et al, 2011).

Belimumab treatment at a dose of 10 mg/kg in combination with standard SLE therapy demonstrated a statistically significant and clinically meaningful reduction in SLE disease activity vs placebo plus standard SLE therapy at week 52 in 2 Phase 3 clinical studies (HGS1006-C1056/BLISS 76 and HGS1006-C1057/BLISS 52) in subjects with active, autoantibody-positive SLE. While the 2 Phase 3 studies did explore the effect of belimumab on individual organ systems, these findings were limited for the renal organ domain as subjects were excluded if they had severe active lupus nephritis. However, 267 subjects (16%) included in the Phase 3 trials had renal involvement by SELENA SLEDAI (comprising hematuria, proteinuria, pyruia and/or urinary casts). In a post-hoc analysis of the pooled data (Table 1-1), there were trends towards SELENA SLEDAI renal organ domain improvement, especially in the subgroup of subjects who were anti-dsDNA positive and had low C3 and/or low C4 at baseline. There were favorable trends of greater reduction in proteinuria, hematuria, pyuria, and lower renal flare rate in the belimumab treatment groups versus placebo. Understanding whether belimumab plus standard of care can reduce the disease activity in subjects with active lupus nephritis subjects is of interest to prescribing physicians and health authorities.

Table 1-1 Renal endpoints at Week 52-Phase 3 SLE trials

	Phase 3 Studies Pooled		
	Placebo N = 562	**1 mg/kg N = 559**	**10 mg/kg N = 563**
SELENA SLEDAI Renal Improvement[1]			
In patients with the following at baseline:			
Renal involvement[2]	39/92 (42.4%)	43/90 (47.8%)	42/85 (49.4%)
Renal involvement + high activity[3]	37/87 (42.5%)	39/86 (45.3%)	42/82 (51.2%)
Renal involvement + anti-dsDNA+low C4[4]	21/62 (33.9%)	24/60 (40.0%)	28/60 (46.7%)
Proteinuria	(n = 116)	(n = 110)	(n = 112)
Median % reduction[5]	27.5	48.3	39.1
Renal Flare			
Subjects with renal flare[6]	16 (2.8%)	14 (2.5%)	8 (1.4%)
Relevant Biomarkers			
Anti-dsDNA[7]			
Positive to Negative	19/280 (6.8%)	47/314 (15.0%)	50/313 (16.0%)
C3[8]			
Low to Normal/High	30/176 (17.0%)	51/193 (26.4%)	77/202 (38.1%)
C4[9]			
Low to Normal/High	40/218 (18.3%)	86/246 (35.0%)	115/259 (44.4%)

1 SELENA SLEDAI renal domain includes hematuria, proteinuria, pyuria, and urinary casts.

2 In subjects with renal involvement at baseline (dropout=failure).

3 In subjects with renal involvement and SELENA SLEDAI score ≥ 7 at baseline (dropout=failure).

4 In subjects with renal involvement and anti-dsDNA+/low complement at baseline (dropout=failure).

5 In subjects with > 0.5 g at baseline (LOCF).

6 Censored at last assessment or start of rescue medications.

7 Anti-dsDNA: Positive (≥ 30 IU/mL); Negative (< 30 IU/mL).

8 C3: Normal/High (≥ 900 mg/L); Low (< 900 mg/L).

9 C4: Normal/High (≥ 16 mg/dL); Low (< 16 mg/dL).

TE24.1, TE26.1, TE26.2 (C1056); TE24.1, TE26.1, TE26.2 (C1057); TA46.7, TAC790, TAC340, TAC397, TA1 (ISE)

In the 2 Phase 3 studies, several clinical measures of improvement including the primary efficacy endpoint at Week 52 (SRI), SELENA SLEDAI reductions, severe flare risk reduction, and complement normalization generally favored the 10 mg/kg dose. Trends toward clinically significant steroid reduction were present for both doses. Additionally, there appeared to be a greater dose response in subjects with high disease and serological activity than in subjects with lower activity. There was no apparent dose-response in the safety profile of belimumab, with both doses being generally well-tolerated, further supporting the selection of 10 mg/kg belimumab as the recommended dose in combination with standard therapies.

The current study is designed to evaluate the efficacy (ie, induction and maintenance of renal remission) and safety of 10 mg/kg belimumab administered IV in combination with standard of care (including MMF, CYC, corticosteroids and AZA) in subjects with active lupus nephritis.

1.4. Benefit-Risk Assessment

1.4.1. Risk Assessment

Belimumab administered by IV infusion is indicated for reducing disease activity in adult patients with active autoantibody positive SLE who are receiving standard therapy. The benefit/risk profile of belimumab for SLE remains favorable. Identified risks include hypersensitivity/infusion reactions and infections. Potential risks (i.e., based on pharmacology but no association identified to date) include progressive multifocal leukoencephalopathy (PML), malignancies, immunogenicity, effects on immunizations (including interactions with live vaccine), and psychiatric events including depression and suicidality. The most common AEs reported in the primary safety population of adults with SLE were associated with hypersensitivity/infusion related reactions, non opportunistic infections, and symptoms consistent with SLE. The majority of reports of infusion-related and hypersensitivity reactions were non-serious and include symptoms such as nausea, vomiting, diarrhea, chills, fever, rash, urticaria, pruritus, headache, dizziness, and dyspnea. However, infusion and hypersensitivity reactions can be severe and fatal. Infections were commonly reported events with belimumab and are expected due to the mechanism of action of belimumab and the SLE patient population.

In the post-marketing setting with IV belimumab, delayed onset of symptoms of acute hypersensitivity reactions as well as recurrence of clinically significant reactions after initial appropriate treatment has been observed. Subjects will remain at the clinic for 3 hours following the first 2 infusions for observation. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. Subjects should be made aware of the potential risk for severe or life-threatening hypersensitivity reactions, the signs and symptoms of such reactions, the potential for delayed onset or recurrence of symptoms, and the importance of immediately seeking medical attention should they occur. Belimumab should be administered by a healthcare professional prepared to treat hypersensitivity reactions including anaphylaxis.

Table 1-2 provides a summary of key issues, their impact, and strategy to mitigate risk in this study.

Table 1-2 Summary of Key Issues, Their Impact and Strategy to Mitigate Risk

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
Post-injection systemic reactions and Hypersensitivity	Administration of belimumab may result in infusion and hypersensitivity reactions, which can be severe and can be fatal. Non-serious infusion reactions and hypersensitivity reactions are common in SLE clinical trials with IV belimumab. Serious infusion and hypersensitivity reactions affected less than 1% of patients and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnea. Delay in the onset of hypersensitivity reactions have been observed. Infusion reactions following administration of belimumab occurred more frequently on the first 2 infusion days and tended to decrease with subsequent administrations. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema.	Exclusion of subjects with a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.	Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. Otherwise, subjects will be monitored during and after each infusion according to study sites' guidelines or standard operating procedure for IV infusions. This may include, but is not limited to, monitoring vital signs and observing for any untoward reactions. Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Belimumab should be administered by a healthcare professional prepared to treat hypersensitivity reactions including anaphylaxis. Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion.

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
Infections	Infections occurred in a slightly greater proportion of subjects treated with belimumab compared with placebo. Infections occurring in at least 3% of patients receiving belimumab and at least 1% more frequently than patients receiving placebo were nasopharyngitis, bronchitis, pharyngitis, cystitis, and gastroenteritis viral. Serious infections occurred in 5% of patients receiving either belimumab or placebo.	Exclude patients who are currently on any suppressive therapy for acute or chronic infection, hospitalized for treatment of infection within 60 days of Day 0, or who used parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days prior to Day 0.,a history of or positive test at screening for HIV, Grade 3 or 4 lymphopenia, Grade 3 or 4 IgG or IgA deficiency, serologic evidence of Hepatitis B viral (HBV) infection based on the results of testing for HBsAg and Anti-HBc including HBsAg positive, HBsAg negative but positive for Anti-HBc regardless of Anti-HBs antibody status requiring clarification by HBV DNA, HBV DNA HCV positive at screening.	Monitor patients for signs and symptoms of infection, monitor laboratory values, request that patients report signs of infection. Treat infections immediately and appropriately. Delay or withhold the dose of study agent, or discontinue study treatment when necessary.

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
Progressive multifocal leukoencephalopathy	No association between belimumab and the risk of opportunistic infections, including PML, has been indentified to date, but data are limited. PML resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab.	Exclude patients who have acute or chronic infection including PML.	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 immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.
Malignancies	As with other immunomodulating agents, the mechanism of action of belimumab may increase the potential risk for the development of malignancies. Across all SLE trials as of 08 March 2013, the relative rate of malignant neoplasms per 100-subject years (excluding non-melanoma skin cancer [NMSC]) for belimumab was 0.527, 95% CI: 0.365-0.736. This rate is consistent with the rate of malignant neoplasms, excluding NMSC, observed in the SLE international cohort (0.53, 95% CI: 0.48, 0.59); incidence ratio 0.87 (0.59, 1.29) (Bernatsky et al, 2005). Incidence rates of malignancy for	Exclude patients with a history of malignant neoplasm within the last 5 years, except for adequately treated basal or squamous cell cancers of the skin, or carcinoma in situ of the uterine cervix.	Monitor patients for signs and symptoms of malignancy, monitor laboratory values, request that patients report signs and symptoms. Treat appropriately.

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
	spontaneous SLE cases were not reported, as the number of cases is too few.		
Immunogenicity	As with other monoclonal antibodies, treatment with belimumab could lead to the development of anti-drug antibodies (ADA). Among SLE subjects treated with belimumab, the proportion of subjects who developed persistently positive ADA was low and very few of the persistently positive antibodies were found to be neutralizing. Neither development of ADA nor persistent ADA was associated with infusion or hypersensitivity reactions. As expected, the proportions of subjects with persistent ADA increased slightly over time in belimumab-treated subjects but (there was no increase in the number of subjects with neutralizing antibodies or the number reporting infusion-related adverse events.	Not applicable	Analyse anti-drug antibody laboratory values at the end of the study to further investigate clinical relevance.

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
Effects on immunizations including reactions with live vaccines	No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving belimumab. Because of its mechanism of action, belimumab may interfere with the response to immunizations. The efficacy of concurrent vaccination in patients receiving belimumab is not known. Limited data suggest that belimumab does not significantly affect the ability to maintain a protective immune response to immunizations received prior to administration of belimumab.	Exclude patients who have received a live vaccine within 30 days of Day 0.	Live vaccines should not be given for 30 days before or concurrently as clinical safety has not been established. Subjects who require a live vaccine during the study should have study agent discontinued prior to receiving the live vaccine.
Potential psychiatric events - Depression and suicidality	There have been reports of depression and suicidality in patients receiving belimumab. Based on an estimated current clinical trial exposure of 7117.3 patient-years (PY) in belimumab studies (as of 08 March 2013), the rate of completed suicide in patients exposed to belimumab in clinical trials is estimated to be 4/7117.3 or 0.056/100 PY (0.015, 0.144). The rate of suicidal behavior (completed suicide and attempt; including overdose) is 15/7117.3 or 0.211/100PY (0.118, 0.348). The rate of suicidal ideation (including all events of suicidality,	Exclude patients who 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 Columbia Suicide Severity Rating Scale [C-SSRS in the last 2 months or who in the investigator's judgment, pose a significant suicide risk.	Monitor patients for signs and symptoms of psychiatric events including depression and suicidality, request that patients report signs and symptoms. Treat appropriately

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
	suicidal thoughts and behavior) is 19/7117.3 or 0.267/100PY (0.161, 0.417). The estimated rates of suicidality for belimumab remain consistent with the rates of the background SLE population. The background rate for completed suicide identified in the literature ranged from 0.02 to 2.18 per 100 PY and varied by study type (clinical trial or observational study) (Li-Yu, 2007; Cervera, 2003; Cervera, 2006; Cervera, 2009). The background rate for suicidal behavior (completed suicide and attempts) is 0.12 (95% CI 0.05, 0.24)/100 patient years (Karassa 2003).		

An Independent Data Monitoring Committee (IDMC) reviews unblinded safety data for this Phase 3 study on an ongoing basis until the data are locked and analyzed through Week 104. At all times the sites and sponsor will remain blinded to treatment allocation. Events to be monitored during the safety review include, at a minimum, all serious adverse events (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 and open-label extension portions of the study. Investigators (and IRBs/IECs, as appropriate,) will be notified of the outcome of each IDMC meeting.

1.4.2. Benefit Assessment

The primary data supporting efficacy of belimumab were the Phase 3 trials (C1056 and C1057) in which 1,684 subjects including those patients with renal manifestations were treated for up to 52 weeks (C1057) or 76 weeks (C1056) (Belimumab IB, Section 5.3.1.2). Belimumab produced significant improvements in the SLE Responder Index as well as in individual component SELENA-SLEDAI score in both studies. Pooled analyses demonstrated steroid sparing, delay in median time to first flare, and decreased risk of severe flares over 52 weeks. In a post hoc analysis of the pooled data in subjects with renal involvement at baseline, there were favorable trends of greater reduction in proteinuria, hematuria, pyuria, and lower renal flare rate with belimumab. These preliminary findings in patients with renal involvement support that belimumab may provide potential benefit to these patients (Dooley et al, 2013). 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 IB, Section 5.3.1.3; Dooley et al, 2013).

1.4.3. Overall Benefit:Risk Conclusion

The safety profile of belimumab remains consistent with that known at approval and is consistent with expected events based on the mechanism of action and the disease under study. Appropriate risk mitigation measures are in place; rare and long-term risks will be further evaluated via the large safety study and registry, ongoing and future studies, and routine pharmacovigilance. Review of safety data is conducted on a continual basis in order to identify new safety signals which may arise from clinical trial and/or post-marketing reports. The benefit: risk profile of belimumab for SLE continues to be favorable. In addition, the preliminary evidence suggests that patients with lupus nephritis may potentially benefit from belimumab.

2. STUDY OBJECTIVES

- To evaluate the efficacy of belimumab in combination with standard of care in adult subjects with lupus nephritis Class III, IV, or V using the 2003 ISN/RPS criteria.
- To assess the safety and tolerability of belimumab plus standard of care versus placebo plus standard of care in adult subjects with lupus nephritis Class III, IV, or V using the 2003 ISN/RPS criteria.

3. STUDY DESIGN

3.1. Basic Design Characteristics

This is a Phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of IV belimumab 10 mg/kg plus standard of care compared to placebo plus standard of care in adult subjects with active lupus nephritis.

Subjects who meet the eligibility criteria during screening will be randomized to 1 of 2 treatment groups in a 1:1 ratio: 10 mg/kg belimumab plus standard of care or placebo plus standard of care. The randomization of all eligible subjects will be stratified by their induction regimen (high dose cortiocsteroids [HDCS] plus CYC vs HDCS plus MMF) and race (black race vs other). Subjects will be dosed with study agent on Days 0 (baseline), 14, 28, and then every 28 days thereafter through 100 weeks with a final evaluation for the double-blind treatment period at 104 weeks. At least 400 and up to approximately 464 lupus nephritis subjects will be randomized with a target of at least 200 and up to approximately 232 subjects in each treatment group (belimumab or placebo). All subjects will receive background therapy consisting of one of the following standard of care regimens:

- High Dose Corticosteroids (HDCS) + Cyclophosphamide (CYC) for induction therapy followed by Azathioprine (AZA) for maintenance therapy

  OR

- HDCS + Mycophenolate Mofetil (MMF) for induction followed by MMF for maintenance therapy

The standard of care medications are described in Section 5.5.1.

All subjects should start the above induction therapy within 60 days prior to or on Day 0 (baseline visit). This will allow subjects to be screened and potentially enrolled and will not be excluded on the basis of necessary acute management. The primary efficacy endpoint of a renal response will be a composite endpoint including changes in proteinuria and renal function at Week 104. For the renal function assessments at all study visits, the glomerular filtration rate (GFR) will be estimated using the simplified MDRD formula and the urinary protein: urinary creatinine ratio will be used for proteinuria. In addition, at baseline, Week 24, 48, 52, 76, 100 and 104, GFR will be calculated based on the mean value of 2 contiguous 24 hour urine collections and 2 serum creatinine measurements. The first serum creatinine will be collected at the initial visit which will take place within 3 days prior to or on the day of the scheduled visit. At the initial visit, subjects will be provided with the materials for collecting the two 24 hour urine collections beginning the next morning following their initial clinic visit. On the third day following the initial visit, subjects will return to the clinic for the second serum creatinine sample. Urine collection may be postponed up to 14 days at the investigators discretion if menstrual bleeding or a genitourinary tract infection is present at any time during the 24 hour urine collection.

The primary endpoint will be measured using the Primary Efficacy Renal Response (PERR) based on study defined criteria (see Section 8.5). Week 104 PERR will be defined by a response at Week 100 that is confirmed by a repeat measurement at Week 104. Likewise, for the relevant major secondary endpoints, complete and ordinal renal responses at Week 104 will be defined by the complete and ordinal renal response at Week 100 that is confirmed by a repeat measurement at Week 104.

All subjects who discontinue treatment with study agent during the double-blind period (for reasons other than withdrawal of consent) should return for all scheduled visits through Week 104.

In the event that a subject withdraws consent from the study, an attempt should be made to obtain consent to collect follow-up safety data (at an exit visit approximately 4 weeks after the last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent) and to obtain survival status at Week 104. Any subject that withdraws consent for use and disclosure of research-related health information will be considered withdrawn from the study and will not be followed for mortality.

Subjects who receive treatment with study agent through Week 100 and complete Week 104 assessments in the double-blind period may enter into a 6-month open-label extension. The Week 104 visit of the double-blind period will serve as the Day 0 visit for subjects entering the 6-month open-label extension. In the open-label extension, all subjects will receive 10 mg/kg belimumab every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the last dose). The first dose on the open-label extension will be given at the Week 104 visit of the double-blind period following the completion of all Week 104 assessments. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety as per the study calendar (see Table 6-3). Subjects who complete the 104-week double-blind period, but do not enter the open-label extension will be required to return for an additional follow up visit 8 weeks after the last dose of study agent. All subjects who enter the open-label extension period and withdraw early will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent.

At the end of the 6-month open-label extension period, subjects who wish to continue treatment may do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may continue to receive belimumab under a separate continuation protocol if permissible according to local regulations. A separate informed consent will need to be provided for the continuation protocol. The 8 week follow-up visit is not required for subjects entering the continuation protocol.

4. INCLUSION AND EXCLUSION CRITERIA

4.1. Inclusion Criteria

Subjects enrolled in the study must meet the following inclusion criteria:

1. Males or females at least 18 years of age.
2. Have a clinical diagnosis of systemic lupus erythematosus (SLE) according to the American College of Rheumatology (ACR) criteria (Appendix 1).
3. Have active, biopsy-proven proliferative lupus nephritis Class III or IV [excluding Class III(C), IV-S(C), and IV-G(C)] either with or without the presence of Class V, or pure Class V membranous using the 2003 ISN/RPS criteria (Appendix 2); the biopsy must be performed in the 6 months prior to the screening visit or during the screening period. The local biopsy report will be used to confirm subject eligibility. A tissue sample from the renal biopsy used to qualify the subject for randomization needs to be sent to a central reading center after Day 0 (baseline).
4. Have unequivocally positive anti-nuclear antibody (ANA) test results defined as an ANA titer ≥ 1:80 (based on Hep-2 immunofluorescence assay or equivalence by enzyme immunoassay assay) and/or a positive anti-dsDNA (≥ 30 IU/mL based on ELISA assay) serum antibody test at the screening visit based on the study's central laboratory results.
5. Have documentation of active renal disease at screening requiring induction therapy with high dose corticosteroids (HDCS) with either IV cyclophosphamide (CYC) or mycophenolate mofetil (MMF) or other oral forms of mycophenolate. The following factors will be used to define active renal disease at screening:
    - Urinary protein:creatinine ratio of ≥ 1.0 AND
        - Active urinary sediment as defined by at least 1 of the following (in absence of menses and genitourinary tract infection).
            - > 5 red blood cell (RBC)/high power field (hpf) or above the laboratory reference range
            - > 5 white blood cell (WBC)/hpf or above the laboratory reference range.
            - Presence of cellular casts (RBC or WBC).
        - Subjects without active urinary sediment are eligible if they meet at least 1 of the following criteria:
            - Have a confirmatory biopsy performed within 3 months prior to the screening visit or during the screening period meeting the criteria outlined in Inclusion Criterion 3.
            - Have proteinuria ≥ 3.5 grams/day (or urinary protein:creatinine ratio≥ 3.5).
6. Have active renal disease defined as above which requires induction therapy with high dose corticosteroids (HDCS) with either intravenous (IV) cyclophosphamide (CYC) or mycophenolate mofetil (MMF) or other oral forms of mycophenolate:

Induction therapy may begin before Screening but should be initiated within 60 days prior to or on Day 0 (baseline). Initiation of induction is when both HDCS and either MMF or CYC have been started.

The study recommended doses for induction therapy are as follows, adjustments may be made for tolerability issues (refer to Section 5.5.1 Standard of Care Medication for details):

- MMF 1-3g/day orally or Mycophenolate sodium 720 - 2160 mg/day orally
- corticosteroids: 0-3 IV pulses of methylprednisolone 500 -1000 mg/pulse followed by oral prednisone 0.5-1.0 mg/kg/day with total daily dose up to 60 mg/day (or equivalence)
- CYC 500 mg by IV infusion every 2 weeks (± 3 days) for 6 infusions

Subjects who have been on MMF for SLE including lupus renal disease may be eligible if they have received, or will receive, the following induction therapy within 60 days prior to or on Day 0 (baseline):

- initiation of HDCS with MMF dose increase to reach the target dose for induction in the subject (if the subject did not previously fail MMF induction based on the investigator's opinion), OR
- initiation of HDCS with discontinuation of MMF and initiation of CYC.

Note: It is recommended that subject eligibility should be discussed with the Medical Monitor if a subject initiated but did not complete an induction therapy within 6 months prior to the initiation of current induction therapy for the study.

7. A female subject is eligible to enter the study if she is:
   - Not pregnant or nursing;
   - Of non-childbearing potential (ie, women who had a hysterectomy, are postmenopausal which is defined as 1 year without menses, have both ovaries surgically removed, or have current documented tubal ligation or any other permanent female sterilization procedure); or
   - Of childbearing potential (ie, women with functional ovaries and no documented impairment of oviductal or uterine function that would cause sterility). This category includes women with oligomenorrhoea [even severe], women who are perimenopausal, or have just begun to menstruate. These women must have a negative serum pregnancy test at screening, and agree to 1 of the following:
     - Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent; or
     - Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during study, and for 16 weeks after the last dose of study agent:
       - Implants of levonorgestrel or etonogestrel;
       - Ethinyl estradiol/Etonogestrel vaginal ring;

- Injectable progesterone;
- Any intrauterine device (IUD) with a documented failure rate of less than 1% per year;
- Oral contraceptives (either combined or progesterone only);
- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) with spermidical foam/gel/film/cream/suppository;
- Transdermal contraceptive patch;
- Male partner sterilisation with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

Note: 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.

8. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study protocol procedures (including required study visits).

4.2. Exclusion Criteria

Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Subjects who have previously failed both CYC and MMF (or other forms of mycophenolate) induction therapies based on the investigator's opinion. If a subject has failed only 1 of the 2 therapies for induction, they may be eligible for study inclusion if the other induction therapy is initiated within 60 days prior to or on Day 0 (ie, a subject who failed MMF is eligible if newly initiating induction therapy with CYC or a subject who failed CYC is eligible if newly initiating induction therapy with MMF).
2. Subjects who received an induction therapy with CYC within 3 months prior to the planned initiation of the current induction for the study.
3. Subjects who receive CYC whose pre-induction leukocyte count is Grade 3 or 4 based on the Adverse Event Severity Grading Tables (Appendix 7).
4. Known hypersensitivity or contraindication to any drug products or any component of these drug products they plan to receive (eg, CYC, MMF, AZA, corticosteroids).
5. Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.
6. Have received treatment with belimumab within 364 days of baseline (Day 0).
7. Received the following within 364 days of baseline (Day 0):

- Nitrogen mustard
- Chlorambucil
- Vincristine
- Procarbazine
- Etoposide
- Abatacept
- Treatment with any B cell targeted therapy (eg, rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI-Fc, or LY2127399 [anti-BAFF])
- A biologic investigational agent (eg, abetimus sodium, anti-CD40L antibody [BG9588/ IDEC-131]). Investigational agent applies to any drug not approved for sale in the country in which it is being used.
- Treatment with interleukin-6 targeted therapy (e.g., tocilizumab, sirukumab).

8. Received any of the following within 90 days of baseline (Day 0):
   - Anti-TNF therapy (eg, adalimumab, etanercept, infliximab, certolizumab, golimumab pegol)
   - Interleukin-1 receptor antagonist (anakinra).
   - Intravenous immunoglobulin (IVIG).
   - Plasmapheresis.
9. Received a non-biological investigational agent within 60 days of baseline (Day 0).
10. Received a live vaccine within 30 days of baseline (Day 0).
11. 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 baseline (Day 0).
12. Have a history of a major organ transplant (eg, heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant or are due to receive transplantation.
13. Subjects who have been on dialysis within 364 days of baseline (Day 0).
14. An estimated glomerular filtration rate < 30 mL/min/1.73 m^2 at the screening visit (using the simplified Modification of Diet in Renal Disease [MDRD] equation).
15. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to SLE (ie, cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, 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 a planned surgical procedure or a history of any other medical disease (eg, cardiopulmonary), laboratory abnormality, or condition (eg, poor venous access) that, in the opinion of the principal investigator, makes the subject unsuitable for the study.
17. Have a history of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix.

18. Have acute or chronic infection requiring management, as follows:
    - Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster, or atypical mycobacteria).
    - Hospitalization for treatment of infection within 60 days of baseline (Day 0).
    - Have had infection requiring treatment with parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of baseline (Day 0).
19. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to baseline (Day 0).
20. Have a historically positive test or test positive at screening for HIV antibody.
21. Hepatitis B: Serologic evidence of Hepatitis B (HB) infection based on the results of testing for HBsAg, anti-HBc and anti-HBs as follows:
    - Patients positive for HBsAg are excluded.
    - Patients negative for HBsAg but positive for Anti-HBc, regardless of Anti-HBs antibody status, will require clarification of their status by testing for HBV DNA
    - o if HBV DNA positive, patients will be excluded from participation
    - o if HBV DNA negative, patients will be eligible to enrol.
    - NOTE: For those subjects randomised, additional ongoing assessment during the study is required (see Section 6.7.5).
22. Hepatitis C: Positive test for Hepatitis C antibody confirmed on a subsequent blood sample by RNA-PCR assay. Subjects who are positive for Hepatitis C antibody and negative when the Hepatitis C RNA-PCR assay is performed on a subsequent sample will be eligible to participate. Subjects who are positive for Hepatitis C antibody and have a positive result for the HCV when the Hepatitis C RNA-PCR assay is performed on the subsequent sample will not be eligible to participate. Subjects in China with positive test for Hepatitis C antibody will be excluded without confirmatory Hepatitis C RNA-PCR testing.
23. Have an IgA deficiency (IgA level < 10 mg/dL).
24. Have a Grade 3 or greater laboratory abnormality (including serum IgG level) based on the Adverse Event Severity Grading Tables (Appendix 7) except for the following that are allowed:
    - Urinalysis (eg, proteinuria)
    - Hematuria
    - Pyuria
    - Casts
    - Hypoalbuminemia due to lupus nephritis.
    - Stable Grade 3 prothrombin time (PT) secondary to warfarin treatment.

- Stable Grade 3 partial thromboplastin time (PTT) due to lupus anticoagulant and not related to liver disease or anti-coagulant therapy.
- Stable Grade 3 gamma glutamyl transferase (GGT) elevation due to lupus hepatitis, and not related to alcoholic liver disease, uncontrolled diabetes or viral hepatitis. If present, any abnormalities in the ALT and/or AST must be ≤ Grade 2.
- Stable Grade 3 reduction in hemoglobin levels due to SLE
- Stable Grade 3 neutropenia or stable Grade 3 white blood cell count [with the exception of subjects receiving CYC who will be excluded if WBC is Grade 3 or 4 per Exclusion Criterion 3]. Note that WBC count should be obtained immediately prior to starting induction therapy. If immediate pre-induction WBC is not available, a WBC count obtained within 28 days prior to induction may be used.
- Hyperuricemia or blood urea nitrogen (BUN) elevation due to lupus nephritis or SLE.

25. Subjects who 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 Columbia-Suicide Severity Rating Scale (C-SSRS) (Appendix 8) in the last 2 months or who, in the investigator's opinion, pose a significant suicide risk.

5. STUDY TREATMENT REGIMEN

5.1. Study Agent Name and Formulation

The common name of the study agent is BENLYSTA™. The generic (USAN/INN) name is belimumab.

Belimumab is a recombinant, human, IgG1λ monoclonal antibody specific for soluble human B lymphocyte stimulator (BLyS, also referred to as BAFF and TNFSF13B). Belimumab has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

Belimumab drug product is provided as a sterile, lyophilized product. Upon reconstitution with 4.8 mL sterile water for injection (SWFI), each vial will contain 80 mg/mL belimumab in 0.16 mg/mL citric acid, 2.7 mg/mL sodium citrate, 80 mg/mL sucrose, 0.4 mg/mL polysorbate 80, pH 6.5. Each lyophilized vial is single use.

The placebo control is prepared as a sterile and lyophilized product. Upon reconstitution with 4.8 mL SWFI, each vial will contain 0.16 mg/mL citric acid, 2.7 mg/mL sodium citrate, 80 mg/mL sucrose, 0.4 mg/mL polysorbate 80, pH 6.5. Each lyophilized vial is single use.

5.2. Packaging, Labeling, Preparation, and Storage

Belimumab will be supplied in a 20 mL vial containing 400 mg belimumab (deliverable).

Placebo control will be supplied in a 20 mL vial.

Lyophilized belimumab and placebo should be stored at 2-8°C. After reconstitution and dilution in normal saline, the material is stable for up to 8 hours at 2-8°C, or at room temperature. Refer to the Pharmacy Manual for detailed instructions on the preparation, administration, and storage of study agent.

The 400 mg single use vial of study agent will be reconstituted with 4.8 mL SWFI, to yield a final concentration of 80 mg/mL of belimumab. Placebo will be reconstituted with 4.8 mL SWFI.

In addition to any country-specific requirements, the study agent label will contain, at a minimum, the following information:

- Product name
- Concentration
- Lot number
- Storage conditions
- Investigational drug statement
- Manufacturer's name and address

The calculated dose of study agent to be administered to the subject is determined in milligrams (mg) using the subject's current body weight in kilograms (kg) which should be obtained at each visit prior to dosing.

The reconstituted study agent will be diluted in 250 mL normal saline for IV infusion. An amount of normal saline, equal to the calculated amount of product to be added (refer to the Pharmacy Manual for additional details), should be removed from the infusion bag prior to adding the product. After adding the reconstituted product, gently invert the bag to mix the solution.

Belimumab and placebo will be supplied as open-label vials and 3rd party unblinding will be employed. The study agent will be reconstituted and diluted by the unblinded site pharmacist or designee, independent of the study (person responsible for receiving and dispensing study agent). Except for a limited number of safety oversight personnel, all other site personnel, the subject, the sponsor, and contract research organization (CRO) will remain blinded to the study agent received and to certain biomarkers and pharmacodynamic laboratory results (see Section 6.7 and Section 6.9). Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

Study agent inventory/accountability forms will be examined and reconciled by the unblinded monitor or designee as long as the study is blinded. After the end of the study

all used and unused study agent must be accounted for on a study agent accountability form provided to the investigator by the sponsor, or its designee.

Refer to the Pharmacy Manual for more details regarding storage, handling, and drug accountability.

5.3. Dose, Route of Administration, and Schedule

The treatment groups include one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving standard of care therapy (as described in Section 5.5.1). All study agent treatments will be administered intravenously over at least 1 hour. Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days days thereafter through 100 weeks of double-blind treatment. Following the final double-blind visit at Week 104, subjects who complete 100 weeks of treatment with study agent and complete Week 104 assessments, will have the option to continue in the 6-month open-label extension period (with first dose given at the Week 104 visit).

Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion. Antihistamine H2-receptor antagonists (eg, ranitidine) are also permitted.

Study agent should be administered by investigators/site personnel prepared to manage infusion reactions and anaphylaxis. In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment period and the open-label extension. The infusion rate may be slowed or interrupted if the subject develops an infusion reaction. Investigators/site personnel should be aware of the risk of hypersensitivity reactions, which may present as infusion reaction, and monitor subjects closely. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. In the event of a serious reaction, study agent administration must be discontinued immediately and the appropriate medical therapy administered. In addition, delayed-type, non-acute hypersensitivity reaction have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial edema Beyond the first 2 infusions, subjects should be monitored during and for an appropriate period of time after infusion according to study sites' guidelines or standard operating procedure for IV infusions. This may include, but is not limited to, monitoring vital signs and observing for any untoward reactions. Subjects should be made aware of the potential risk, the signs and the symptoms of such reactions, and the importance of immediately seeing medical attention.

5.4. Alteration of Dose/Schedule Due to Toxicity

The dose of study agent administered may not be altered. The rate of infusion may be slowed or interrupted if the subject appears to develop signs of adverse reaction or infusion-associated symptoms. At later visits, these subjects may continue to be infused over a longer infusion period at the investigator's clinical discretion.

If a subject experiences a clinically significant AE that the investigator believes may be definitely, possibly or probably related to study agent and could potentially be exacerbated by the next dose, the investigator may delay the dose by up to 2 weeks or withhold 1 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 study agent should be discontinued.

If a subject experiences a clinically significant, potentially *life-threatening* (Grade 4) AE that the investigator believes may be definitely, possibly or probably related to study agent, then treatment with study agent will be discontinued. The subject should be withdrawn from study agent, and followed at regularly scheduled study visits as specified by protocol and also until resolution of the AE(s) (whichever is longer). All subjects should be monitored closely for infection. Increased vigilance for infection is recommended in subjects whose serum IgG concentrations are < 250 mg/dL. Clinical judgment should be applied with respect to the appropriateness of continuing study therapy in these subjects. If a subject experiences IgG levels < 250 mg/dL, the dose of study agent must be withheld and the Medical Monitor must be consulted before administering any subsequent dose of study agent. Study agent will be discontinued in subjects with IgG levels < 250 mg/dL that are associated with a severe or serious infection.

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. 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 immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

5.5. Concurrent Medications During the Double-blind Treatment Period

This section reviews medications which are required or allowed provided the guidelines below are followed. Anytime the concurrent medication requirements are not followed, the subject will have study agent discontinued and will be considered a treatment failure (non-responder).

Whenever possible, a complete disease activity assessment (SELENA SLEDAI, SLE Flare Index and PGA) and laboratory assessments (hematology, chemistry, urinalysis, anti-dsDNA, and complement) should be performed to document renal flare *prior* to instituting treatment that results in treatment failure designation.

Comprehensive education and guidance regarding the use of concurrent standard of care medications (including escalations and tapers, as appropriate) must be provided to the

subject at baseline (Day 0) and each scheduled visit. Subject compliance with concurrent medications is essential and will be monitored and recorded in the eCRF. Guidance for subject education and instructions regarding monitoring subject compliance will be provided in the Study Procedures Manual.

Received doses for all systemic corticosteroids are considered as prednisone equivalent. As such, when "prednisone" is used throughout this protocol, it refers to prednisone dose or equivalent.

5.5.1. Standard of Care Medication

This section reviews the required induction and maintenance standard of care regimens. All subjects should receive background standard of care therapy consisting of either CYC plus HDCS for induction followed by AZA for maintenance or MMF plus HDCS for induction followed by MMF for maintenance. Each investigator must refer to the country-specific label for each required medication and heed appropriate warnings and precautions. If in the clinical judgment of the investigator, infection (including active or latent tuberculosis [TB] and active HBV infection) is suspected in a subject, screening examinations and appropriate management before initiating induction therapy should be considered following local guidelines.

The induction and maintenance regimens specified in this protocol are based on accepted clinical paradigms. Because the response of individual subjects to any given regimen cannot be predicted, it is important that the clinical course is monitored closely. If a subject fails to respond in an appropriate timeframe, or their renal function shows clinically significant deterioration, then appropriate rescue therapy should be instituted to minimize the risk of increasing renal damage. Once randomized, such subjects will be considered treatment failures for analysis, but should return for their scheduled visits through Week 104. If any of the standard of care medications as induction and maintenance regimens is discontinued, the Medical Monitor should be consulted to assess the appropriateness of continuing study treatment in these subjects.

Cyclophosphamide and Azathioprine

Cyclophosphamide (CYC) used for induction therapy will consist of 500 mg by IV infusion every 2 weeks (± 3 days) for 6 infusions. Adjustments may be made for tolerability issues. If subjects previously received MMF for treatment of SLE including lupus renal disease and will receive CYC induction, MMF should be discontinued when CYC is initiated.

For the maintenance period, AZA will be started approximately 2 weeks after the last dose of CYC with a target dose of 2 mg/kg/day (not to exceed 200 mg/day) until study end. A prescribed total daily dose should be as close as possible to a target dose of 2mg/kg/day, a total daily dose greater than 200 mg/day is prohibited and considered to constitute treatment failure. It is recommended that dosing commence at 50 mg/day and increase by no more than 50 mg/day every week until the target dose is achieved. Adjustments may be made for tolerability issues. Subjects who develop Grade 3 or 4 leucopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe

gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above a switch to MMF will be permitted. The use of mesna and/or leuprolide (leuprorelin) is permitted with CYC dosing in accordance with the usual practice of the investigator.

Mycophenolate Mofetil

MMF used for induction and maintenance therapy is recommended at a dose from 1-3 g/day orally through study end. The investigator should determine the appropriate dose within the dose range recommended for an individual subject based on the consideration of clinical benefit and side effects that may be expected. Dosing of MMF is recommended to start at 0.5 g twice a day (bid) for the first week, increase to 1 g bid for the second week, and then 1.5 g bid for the third and subsequent weeks, if appropriate. MMF should be taken morning and evening, before meals, with a glass of water. If tolerability issues are experienced with bid dosing, subjects may receive 1 g 3x/day (tid). If tid dosing is not tolerated, the MMF dose may be reduced to as low as 1 g/day. In addition, subjects who develop grade 3 or 4 neutropenia or any other side effects that are considered clinically significant by the investigator following initiation of MMF will be permitted to reduce the dose to no less than 1 g/day. A prescribed dose greater than 3 g/day is prohibited and considered to constitute treatment failure.

After 6 months of MMF therapy, the dose of MMF may be reduced to 1 g/day or subjects may be switched to AZA (target dose 2 mg/kg/day) for tolerability reasons.

If MMF dose has to be temporarily reduced to less than 1g/day for safety reasons (eg. Serious Adverse Event), the Medical Monitor should be consulted to assess the appropriateness of continuing study treatment in the subject.

Mycophenolate sodium may be used in lieu of MMF for induction and/or maintenance therapy. A dose from 720 mg/day to 2160 mg/day orally is recommended. A dose greater than 2160 mg/day is prohibited and considered to constitute treatment failure.

The use of IV forms of mycophenolate is prohibited.

High Dose Corticosteroids

All subjects must be on a daily corticosteroid regimen as part of the induction therapy.

The study recommended corticosteroid regimen includes 0-3 IV pulses of methylprednisolone 500 mg-1000 mg/pulse followed by oral prednisone at a recommended dose of 0.5-1.0 mg/kg/day with total daily dose up to 60 mg/day. Adjustments may be made for tolerability issues. It is recommended that oral corticosteroids be tapered according to Table 5-1. If necessary, it may take longer than 12 weeks to complete the taper.

Note: By Week 24, the dose of corticosteroids must be at 10 mg of prednisone/day or less (can be 0 mg) or subject will be considered a treatment failure.

Table 5-1 Recommended oral prednisone taper regimen

Study Week	Reduced Dose (mg/day)
0	60
2	50
3	45
4	40
5	35
6	30
7	25
8	20
9	17.5
10	15
11	12.5
12	10

5.5.2. Immunosuppressives

The primary objective of this trial is to evaluate the efficacy of belimumab plus standard of care to reduce lupus nephritis disease activity. Other immunosuppressives (eg, methotrexate [MTX]) will be allowed provided these are started prior to baseline and meet eligibility criteria. Dose alterations during the trial of these agents are permitted. Subjects who newly initiate immunosuppressives (with the exception of topical agents) after the baseline visit outside the induction regimen will be considered treatment failures.

5.5.3. Angiotension Pathway Antihypertensives

Drugs acting on the renin-angiotensin system are known to reduce proteinuria and are thought to have a renoprotective effect (Kanda et al, 2005). Therefore, it is strongly recommended that all subjects be receiving angiotensin pathway antihypertensive agents (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor antagonists/blockers [ARBs]), or a combination therapy that includes these agents at screening/baseline and during the study. Since these medications may confound efficacy assessment by mimicking renal deterioration (eg, increased serum creatinine) or improving renal function (eg, beneficial remodeling of renal parenchyma), the following guidelines should be applied:

- Starting a new angiotensin pathway antihypertensive (ACE inhibitor, angiotensin receptor blocker) treatment after the Week 24 visit will cause the subject to be declared a treatment failure.
- An angiotensin pathway antihypertensive will be considered new if the subject did not receive an angiotensin pathway antihypertensive at any time during the Day 0 to Week 24 treatment interval.
- An angiotensin pathway antihypertensive may be replaced with another angiotensin pathway antihypertensive at any time during the study.

- Titration of dose to obtain therapeutic effect on blood pressure is allowed.
- Initiation of new antihypertensive agents other than ACE inhibitors or ARBs is permitted.

5.5.4. Anti-malarials

Hydroxycloroquine use in patients with lupus nephritis has been shown to delay the development of renal damage (Pons-Estel et al, 2009). Therefore, it is strongly recommended that all subjects be receiving hydroxychloroquine at screening/baseline and during the study.

Since these medications may confound efficacy assessment by improving renal function, the following guidelines should be applied:

- a subject starting antimalarial treatment after the Week 24 visit will be declared a treatment failure.
- an antimalarial medication may be replaced with another at anytime during the study.
- dose change is allowed during the study if the antimalarial treatment was initiated by Week 24 visit

5.5.5. Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Aspirin

The use of NSAIDs is not recommended during the study, although use would not constitute a treatment failure.

5.5.6. Corticosteroids

5.5.6.1. Systemic Corticosteroids for Non-renal SLE-related Disease Activity

All subjects should be receiving a corticosteroid dose of 10 mg/day or less (can be 0 mg) by Week 24. Those who cannot be tapered to 10 mg/day or less by Week 24 will be declared treatment failures. No corticosteroid rescue treatment will be allowed from Week 76-104 because the treatment effect may confound the interpretation of study results and the subject will be declared a treatment failure. Outside of this window, there will be a limited number of corticosteroid rescue treatments allowed if clinically indicated for non-renal SLE-related disease activity as outlined below.

- Up to 2 corticosteroid rescue treatments will be allowed.
- At least a 3-month interval is required between each treatment.
- Each treatment course should be no longer than 14 days in duration with the steroid dose returning to $\leq$ 10 mg/day by Day 14.
- Up to a total of 20 mg/day (prednisone or prednisone equivalent) is permitted.
- There can be no concurrent worsening of renal disease.

Any subjects who require corticosteroid rescue treatment exceeding the above criteria or who are unable to return to a dose $\leq$ 10 mg/day will be considered treatment failures.

Additionally, any subjects who have not returned to ≤ 10 mg/day by Week 76 will be considered treatment failures.

5.5.6.2. Systemic Corticosteroids for Renal SLE-related Disease Activity

All subjects should be receiving a corticosteroid dose of 10 mg/day or less (can be 0 mg) by Week 24. Those who cannot be tapered to 10 mg/day or less by Week 24 will be declared treatment failures.

The use of corticosteroids at a dose of > 10 mg/day for treatment of a renal flare (with or without concurrent non-renal SLE disease activity) is prohibited after Week 24 and the subject would be considered a treatment failure.

5.5.6.3. Systemic Corticosteroids for Non-SLE Disease Activity

No corticosteroid rescue treatment will be allowed from Week 76-104 because the treatment effect may confound the interpretation of study results and the subject will be declared a treatment failure. Outside of this window, there will be a limited number of corticosteroid treatments allowed if clinically indicated for the treatment of non-SLE disease activity (eg, allergic reaction).

- Up to 3 corticosteroid treatments will be allowed.
- At least a 3 month interval is required between each treatment.
- The maximum dose should be no longer than 3 days in duration with the steroid dose returning to ≤ 10 mg/day by Day 14.
- Up to a total of 60 mg/day (prednisone or prednisone equivalent) will be permitted.

Any subjects who require corticosteroid rescue treatment exceeding the above criteria or who are unable to return to a dose no more than ≤ 10 mg/day will be considered treatment failures. Additionally, any subjects who have not returned to ≤ 10 mg/day by Week 76 will be considered treatment failures.

5.5.6.4. Intraarticular Injections

Intraarticular injections will be allowed as clinically indicated. However, no intraarticular corticosteroid injections should be given from Week 96-104 although this use would not constitute a treatment failure.

5.5.6.5. Inhaled and Topical Corticosteroids

Inhaled and topical steroids are allowed throughout the course of the study.

5.6. Prohibited Medications and Non-Drug Therapies During the Double-Blind Treatment Period

Subjects who start the prohibited medications or therapies listed below at any time during the double-blind treatment period will be considered treatment failures for analysis (ie, non-responders). These subjects must discontinue treatment with study agent and should

return for scheduled visits through Week 104. The following medications and therapies are prohibited at any time during the double-blind treatment period:

- New immunosuppressant agents (other than described in Section 5.5.1 as part of the induction and maintenance regimens).
- Corticosteroid use outside of the limits described in Section 5.5.6.
- 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.
- Anti-TNF therapy (eg, adalimumab, etanercept, infliximab).
- Other biologics (eg, rituximab, abatacept, interleukin-1 receptor antagonist [anakinra]).
- Intravenous immunoglobulin (IVIG).
- Plasmapheresis.

Whenever a subject has worsening nephritis or SLE, a complete disease activity assessment (SELENA SLEDAI, SLE Flare Index, and PGA) and laboratory assessments (hematology, chemistry, urinalysis, urinary microscopy, spot urine, anti-dsDNA, and complement) should be performed to document disease activity prior to instituting treatment that results in treatment failure designation as defined in Section 5.5 and Section 5.6.

5.6.1. Live Vaccines

Live vaccines are not permitted in the study. Subjects who require a live vaccine during the study should have study agent discontinued prior to receiving the live vaccine. These subjects should continue to return for the scheduled visits through Week 104.

5.7. Prohibited Medications During Open-Label Extension

During the open-label extension, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate. Prohibited medications during this phase are live vaccines, biological therapies, and other investigational agents.

6. STUDY PROCEDURES

The nature of potential risks and benefits associated with participation in the study will be explained to all potential study subjects. Written informed consent (including consent for the use and disclosure of research-related health information) must be obtained before the subject can begin any screening procedures that are not considered part of standard patient care.

Subjects participating in the pharmacogenetics (PGx) research portion of the protocol (Appendix 6) must sign the PGx informed consent prior to any PGx samples being drawn from the subject.

Refer to the Study Calendar (Table 6-1, Table 6-2, and Table 6-3), Study Procedures Manual, and Central Laboratory Manual for additional information.

6.1. Screening Procedures (Day -35 to Day 0)

The following assessments are required at screening:

- Demographics.
- Medical history.
- Therapy History.
- Complete physical examination (including vital signs).
- Confirm diagnosis of SLE disease (based on ACR criteria) by reviewing previously documented clinical records (see Appendix 1).
- Record concurrent medications.
- Blood samples for: (see Appendix 5 – Laboratory Tests)
  - Hematology.
  - Modified Chem 20 (non-fasting).
  - Serum pregnancy test - for all women with an intact uterus, unless exempted from pregnancy testing (ie, of non-childbearing potential - women who had a hysterectomy, are post-menopausal which is defined as 1 year without menses, have both ovaries surgically removed or have current documented tubal ligation or any other permanent female sterilization procedure).
  - Autoantibodies (ANA and anti-dsDNA).
  - Biological markers (Complement C3, C4).
  - Serum immunoglobulin isotypes (IgG, IgM, IgA).
  - HIV antibody testing, serologic investigations for Hepatitis B (HB) infection (HBsAg, anti-HBc, and anti-HBs, HBV DNA, NOTE: if anti-HBc result is reactive, the sample drawn for HBV DNA will be tested for viral DNA; otherwise, the sample will be destroyed), and Hepatitis C antibody testing ± confirmatory HCV RNA-PCR testing. (NOTE: see Section 4.2, subjects in China with positive test for Hepatitis C antibody will be excluded without confirmatory Hepatitis C RNA-PCR testing).
  - PT/PTT
- Urine sample for:
  - Urinary protein: urinary creatinine ratio.
  - Locally performed urinary microscopy and routine urinalysis. Note: Urine collection may be postponed up to 14 days at the investigators discretion if menstrual bleeding or a genitourinary tract infection is present at the time of urinalysis.

- Renal biopsy result (should be from a renal biopsy obtained in the 6 months prior to the screening visit or during the screening period. The local biopsy reports will be used for the purposes of randomization. A tissue sample from the renal biopsy used to qualify the subject for randomization needs to be sent to a central reading center after Day 0 (baseline).
- Pre-flare GFR and/or serum creatinine – most recent GFR and/or serum creatinine values obtained prior to screening and before first manifestations of the current renal flare.
- Suicidality assessment by using the Columbia-Suicide Severity Rating Scale (C-SSRS) Screening assessment form (see Section 7.6 and Appendix 8).
- For subjects in China, SAEs will be collected from the time a subject consents to participate in the study (see Section 7.2).
- Confirm subject meets study entry criteria.

6.2. Study Enrollment Procedures

Subjects who have undergone all screening procedures and have met the entry criteria will be enrolled into the study and assigned to treatment by Interactive Web Response System (IWRS). Subjects will be randomized in a 1:1 ratio to treatment with either 10 mg/kg belimumab plus standard of care or placebo plus standard of care. Randomization of all eligible subjects will be stratified by their induction regimen (HDCS plus CYC vs HDCS plus MMF) and race (black race vs other). There is race stratification in this study because race may be an important factor related to outcomes in patients with lupus nephritis. Race should be self-designated.

6.3. Double-Blind Treatment Period

Subjects will be evaluated during the scheduled study visits as outlined in the Study Calendar (Table 6-1 and Table 6-2). Time windows are provided for each study visit to allow flexibility in site and subject scheduling. All study visits should occur within the visit window of the scheduled study visit.

At baseline (Day 0), the subject will be randomized and receive the first dose of study agent. Visits to the study site for clinical evaluation, disease activity assessment, and laboratory sampling will occur approximately every 28 days (calculated from the Day 0 dose) through Week 104. All efforts should be made to retain subjects on schedule, based on the date of their Day 0 dose. During the double-blind treatment period, study agent is administered at every scheduled visit through Week 100. The final efficacy evaluation for the double-blind portion of the study will occur at Week 104. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.

Subjects who complete the double-blind period through Week 104 will be given the option to receive belimumab in the 6-month open-label extension.

- Subjects who receive treatment with study agent through Week 100 and complete Week 104 assessments, but do not enter the open-label extension, will not have study agent administered at Week 104. Assessments should be completed for the Week 104/Exit visit, and the subject should return in 4 weeks for the Follow-up visit.
- Subjects who wish to continue in the open-label extension, will have study agent administered at the Week 104 visit after all Week 104 assessments are performed (refer to Section 6.4 below). Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions.

All subjects who discontinue treatment with study agent during the double-blind period (for reasons other than withdrawal of consent) should return for all scheduled visits through Week 104.

In the event that a subject withdraws consent during the double-blind treatment period, an attempt should be made to obtain consent to collect follow-up safety data (at an exit visit approximately 4 weeks after the last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent) and to obtain survival status at Week 104. Any subject that withdraws consent for use and disclosure of research-related health information will be considered withdrawn from the study and will not be followed for mortality.

Note that a urine pregnancy test is required at the 8-week follow-up visit for all women with an intact uterus, unless exempted from pregnancy testing (see Section 6.1). Women of child-bearing potential must be reminded of the requirement to report to the study investigator any pregnancy that occurs through 16 weeks following the last dose of study agent (see Section 7.7).

Table 6-1 Study Calendar - Double-Blind Treatment Period (Screening to Week 52)

	Screening	Baseline	Double-Blind Treatment Period																	
Study Day	-35 days	Day 0	Day 3	14 ± 3 days	28 ± 3 days	56 ± 7 days	84 ± 7 days	112 ±7 days	140 ± 7 days	168 ± 7 days		196 ± 7 days	224 ± 7days	252 ± 7days	280 ± 7days	308 ± 7days	336 ± 7days		364 ± 7days	
Study Week	Wk -5			Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	WK 20	Wk 24	Wk 24 + 3d	Wk 28	Wk 32	Wk 36	WK 40	Wk 44	Wk 48	Wk 48 + 3d	Wk 52	Wk 52 + 3d
Written Informed Consent	x																			
Demographics (including race)	x																			
Medical History	x																			
SLE History	x																			
Therapy History	x																			
Eligibility Criteria	x																			
Biopsy Report[A]	x																			
Pre-flare GFR[B]	x																			
Biopsy sample shipment for central evaluation		After Day 0																		
Clinical Assessments																				
SELENA SLEDAI, SLE Flare Index and PGA		x					x			x				x					x	
SLICC Damage		x								x									x	
C-SSRS Screening/Baseline	x																			
C-SSRS Since Last Visit[C]		x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Record Concurrent Medications	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Complete Physical Exam	x																			
Symptom-driven Physical Exam		x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Weight[D]	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Vital signs[P]	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
12-lead ECG		x																		
Record/Assess Adverse Events[E]	x[R]	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Laboratory Assessments																				
Hematology and chemistry (non-fasting)[F]	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Serum Creatinine[G]			x								x							x		x

	Screening	Baseline	Double-Blind Treatment Period																	
Study Day	**-35 days**	**Day 0**	**Day 3**	**14 ± 3 days**	**28 ± 3 days**	**56 ± 7 days**	**84 ± 7 days**	**112 ±7 days**	**140 ± 7 days**	**168 ± 7 days**		**196 ± 7 days**	**224 ± 7days**	**252 ± 7days**	**280 ± 7days**	**308 ± 7days**	**336 ± 7days**		**364 ± 7days**	
Study Week	**Wk -5**			**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**WK 20**	**Wk 24**	**Wk 24 + 3d**	**Wk 28**	**Wk 32**	**Wk 36**	**WK 40**	**Wk 44**	**Wk 48**	**Wk 48 + 3d**	**Wk 52**	**Wk 52 + 3d**
Urinalysis[H]	x	x			x	x	x	x	x	x		x	x	x	x	x	x		x	
Urinary Microscopy[H]	x	x			x	x	x	x	x	x		x	x	x	x	x	x		x	
Spot urine	x	x			x	x	x	x	x	x		x	x	x	x	x	x		x	
24-hour Urine[G]		X								x							x		x	
Urine Biomarkers		x					x			x									x	
BLyS protein (baseline only)		x																		
Pregnancy Test[I]	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
ANA	x	x								x									x	
Complement (C3/C4), anti-dsDNA	x	x			x	x	x	x	x	x		x	x	x	x	x	x		x	
aCL (IgA, IgG, IgM isotypes)		x								x									x	
Anti-Sm, anti-C1q[J]		x								x									x	
Serum IgG	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Serum IgA & IgM	x	x				x				x									x	
PT/PTT	x	x				x				x									x	
HIV, Hep B and Hep C serology, and HBV DNA[Q]	x																			
Pharmacokinetic Sampling[K]		x	x	x	x	x				x	x								x	
Immunogenicity (anti-belimumab antibody)		x				x				x									x	
Peripheral B lymphocytes		x				x				x									x	
Pharmacogenetics Sampling (consenting subjects only)[L]		x																		
Protocol Treatments																				
Study Agent Administration (Belimumab/Placebo)[M,N]		x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Induction/Maintenance Therapy[O]	Throughout the Study																			

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

[B]Most recent GFR prior to the current renal flare.
[C] The Columbia-Suicidality Severity Rating Scale (C-SSRS) Since Last Visit form (see Appendix 9) will be used at Day 0 and all subsequent visits. The C-SSRS Baseline/Screening form (see Appendix 8) is only used at Screening.
[D]The weight at the current visit should be used to calculate dose.
[E]For subjects who discontinue treatment with study agent during the double-blind period (for reasons other than withdrawal of consent), all adverse events will be collected through 8 weeks following the administration of the last dose of study agent. After this time, SAEs, regardless of relationship to study drug, will be collected through Week 104.
[F] Refer to Appendix 5 for a listing of laboratory assessments to be completed.
[G]Two 24 hour urine and serum creatinine collections will be performed for each of the following visits: baseline, Weeks 24, 48 and 52. Serum creatinine for these visits will be collected at the initial visit which will take place within 3 days prior to or on the day of the scheduled visit, and then 3 days after the initial visit. For urinary sediment assessments, both menstrual cycles and genitourinary tract infections may be confounders. Urine collection may be postponed up to 14 days at the investigators discretion if menstrual bleeding or a genitourinary tract infection is present at time of urinalysis or anytime during the 24 hour urine collection.
[H]Routine urinalysis and urinary microscopy will be performed locally.
[I]For women of child-bearing potential, serum pregnancy test is required at screening. At subsequent visits, a urine pregnancy test is required. Results of the pregnancy test must be available prior to dosing.
[J]Samples will only be analyzed in subjects with positive results at baseline.
[K]For PK sampling times, see Section 6.7.1.
[L]Pharmacogenetic sampling informed consent must be obtained prior to any blood being taken for PGx research. Sample should be drawn prior to dosing.
[M]Subjects who are withdrawn from treatment with study agent prior to Week 100 (for reasons other than withdrawl of consent) should continue to follow the study calendar and have all assessments completed through Week 104 (with the exception of study agent administration).
[N] Subjects should remain under clinical supervision for 3 hours after completion of the first 2 study agent infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.
[O]Induction therapy may begin before Screening but should be initiated within 60 days prior to or on Day 0 (baseline).
[P] Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate. On days on which study agent is administred, vital signs are to be performed prior to dosing.
[Q]Note: if anti-HBc result is reactive, the sample drawn for HBV DNA will be tested for viral DNA; otherwise, the sample will be destroyed. Subjects in China with positive hepatitis C screening results will be excluded without confirmatory hepatitis C RNA-PCR testing.
[R]Note: For subjects in China, SAEs will be collected from the time a subject consents to participate in the study (see Section 7.2).

Table 6-2 Study Calendar - Double-Blind Treatment Period (Week 56 to 104)

	Double-Blind Treatment Period																	
Study Day	**392 ± 7days**	**420 ± 7days**	**448 ± 7days**	**476 ± 7days**	**504 ± 7days**	**532 ± 7days**		**560 ± 7days**	**588 ± 7days**	**616 ± 7days**	**644 ± 7days**	**672 ± 7days**	**700 ± 7days**		**Day 728/ Exit [A] ± 7days (4 weeks after last dose)**		**Follow-up visit[B] (8 week after last dose) +7 days**	**Unscheduled Visit[C]**
Study Week	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 76 + 3 d**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 100 + 3 d**	**Wk 104**	**Wk 104 + 3 d**		
Clinical Assessments																		
SELENA SLEDAI, SLE Flare Index and PGA			x			x				x					x			x
SLICC Damage						x									x			
C-SSRS Since Last Visit	x	x	x	x	x	x		x	x	x	x	x	x		x			
Record Concurrent Medications	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Symptom-driven Physical Examination	x	x	x	x	x	x		x	x	x	x	x	x		x			
Weight[D]	x	x	x	x	x	x		x	x	x	x	x	x		x			
Vital signs[N]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Record/Assess Adverse Events[E]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Survival Assessment[F]															x			
Laboratory Assessments																		
Hematology and chemistry (non-fasting)[G]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Serum Creatinine[H]							x							x		x		
Urinalysis[I]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Urinary Microscopy[I]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Spot urine	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
24-hour Urine[H]						x							x		x			
Urine Biomarkers															x			
Pregnancy Test[J]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	
Complement (C3/C4), anti-dsDNA	x	x	x	x	x	x		x	x	x	x	x	x		x			x
ANA, aCL (IgA, IgG, IgM isotypes)						x									x			
Anti-Sm, anti-C1q[K]						x									x			
Serum IgG			x			x				x			x		x			
Serum IgA & IgM						x									x			
PT/PTT						x									x			
Pharmacokinetic Sampling[L]															x		x	

	Double-Blind Treatment Period																	
Study Day	**392 ± 7days**	**420 ± 7days**	**448 ± 7days**	**476 ± 7days**	**504 ± 7days**	**532 ± 7days**		**560 ± 7days**	**588 ± 7days**	**616 ± 7days**	**644 ± 7days**	**672 ± 7days**	**700 ± 7days**		**Day 728/ Exit [A] ± 7days (4 weeks after last dose)**		**Follow-up visit[B] (8 week after last dose) +7 days**	**Unscheduled Visit[C]**
Study Week	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 76 + 3 d**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 100 + 3 d**	**Wk 104**	**Wk 104 + 3 d**		
Immunogenicity (anti-belimumab antibody)						x									x		x	
Peripheral B lymphocytes						x									x			
Protocol Treatments																		
Study Agent Administration (Belimumab/Placebo)[M]	x	x	x	x	x	x		x	x	x	x	x	x		**If entering extension**			
Induction/Maintenance Therapy	Throughout the Study																	

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

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

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

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

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

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

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

[H]Two 24 hour urine and serum creatinine collections will be performed for each of the following visits: Weeks 76, 100 and 104. The serum creatinine for these visits will be collected on the day of the initial visit and then 3 days after the initial visit. For urinary sediment assessments, both menstrual cycles and genitourinary tract infections may be confounders. Urine collection may be postponed up to 14 days at the investigators discretion if menstrual bleeding or a genitourinary tract infection is present at anytime during the 24 hour urine collection.

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

[J]For women of child-bearing potential, a urine pregnancy test is required. Results of the urine pregnancy test must be available prior to dosing.

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

[L]For PK sampling times, see Section 6.7.1.

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

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

6.4. Open-Label Extension

Subjects who receive treatment with study agent through Week 100 and complete the Week 104 assessments in the double-blind period may enter into a 6-month open-label extension. The Week 104 visit of the double-blind period will serve as the Day 0 visit for subjects entering the 6-month open-label extension. In the open-label extension, all subjects will receive 10 mg/kg belimumab approximately every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the last dose). The first dose on the open-label extension will be given at the Week 104 visit of the double-blind period after the completion of Week 104 assessments. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety as per the study calendar (see Table 6-3). Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.

All subjects who withdraw early from the open-label extension will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent.

At the end of the 6-month open-label extension period, subjects who wish to continue treatment may do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may continue to receive belimumab under a separate continuation protocol if permissible according to local regulations. A separate informed consent will need to be provided for the continuation protocol. The 8-week follow-up visit is not required for subjects entering the continuation protocol.

Note that a urine pregnancy test is required at the 8-week follow-up visit for all women with an intact uterus, unless exempted from pregnancy testing (see Section 6.1). Women of child-bearing potential must be reminded of the requirement to report any pregnancy that occurs through 16 weeks following the last dose of study agent (see Section 7.7).

Table 6-3 Study Calendar- 6-Month Open-Label Extension

	Open Label Extension								
Study Day	**Day 0[A]**	**Day 28 ± 7 days**	**Day 56 ± 7 days**	**Day 84 ± 7 days**	**Day 112 ± 7 days**	**Day 140 ± 7 days**	**Day 168 ± 7 days**	**Day 196/Exit[B] ± 7days (4 weeks after last dose)**	**Follow-up visit[C] (8 weeks after last dose) +7 days**
Study Week		**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**WK 20**	**Wk 24**	**Wk 28**	
Clinical Assessments	See Week 104 Visit in Double-Blind Treatment Period								
SELENA SLEDAI, SLE Flare Index and PGA								x	
SLICC Damage								x	
Record Concurrent Medications		x	x	x	x	x	x	x	x
Symptom-driven Physical Examination								x	
Weight[D]		x	x	x	x	x	x	x	
Vital signs[L]		x	x	x	x	x	x	x	x
Record/Assess Adverse Events		x	x	x	x	x	x	x	x
Laboratory Assessments									
Hematology and chemistry (non-fasting)[E]				x			x	x	x
Urinalysis[F]				x			x	x	x
Urinary Microscopy[F]				x			x	x	x
Spot Urine				x			x	x	x
Pregnancy Test[G]		x	x	x	x	x	x	x	x
C3/C4, anti-dsDNA							x	x	
Autoantibodies (aCL, ANA, anti-Sm, anti-C1q)[H]							x	x	
Serum IgG			x				x	x	
Serum IgA & IgM							x	x	
Pharmacokinetic sampling[I]									x
Immunogenicity (anti-belimumab antibody)							x		x
Peripheral B lymphocytes							x	x	
Protocol Treatments									
Study Agent Administration (belimumab)[K]	x	x	x	x	x	x	x		
Maintenance Therapy[J]	Throughout the Study								

[A]Day 0 of the open-label extension is the Week 104 study visit of the double-blind treatment period, and represents the first belimumab administration for those subjects continuing on the 6 month open-label extension.
[B] For subjects who discontinue from the study, an Exit visit should be completed 4 weeks after the last dose of study agent.
[C] For subjects who discontinue from the study, a Follow-up visit should be completed 8 weeks after the last dose of study agent. The 8-week follow up visit is not required for subjects entering the separate continuation protocol.
[D] The weight at the current visit should be used to calculate dose.
[E]Refer to Appendix 5 for a listing of laboratory assessments to be completed.
[F]Routine urinalysis and urinary microscopy will be performed locally.
[G]For women of child-bearing potential, a urine pregnancy test is required. Results of the urine pregnancy test must be available prior to dosing.
[H]Samples will only be analyzed for anti-Sm and anti-C1q in subjects with positive results at baseline.
[I]For PK sampling times, see Section 6.7.1.
[J] AZA/MMF continued at the discretion of the investigator.
[K] Subjects should remain under clinical supervision for 3 hours after completion of the first 2 study agent infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.
[L] Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate. On days on which study agent is administred, vital signs are to be performed prior to dosing.

6.5. Unscheduled Visits

Unscheduled visits may be necessary during the course of the study to capture a subject's status between regularly scheduled visits. Examples include, but are not limited to, a worsening of lupus nephritis symptoms, AE reporting, or follow-up to a previously reported AE.

When a subject has worsening nephritis or SLE, a complete disease activity assessment (SELENA SLEDAI, SLE Flare Index and PGA), and laboratory assessments (hematology, chemistry, urinalysis, urinary microscopy, spot urine, anti-dsDNA, and complement) should be performed to document disease activity worsening (eg, renal flare/relapse) prior to instituting treatment that results in treatment failure designation as defined in Section 5.5 and Section 5.6.

Refer to the Study Calendar (Table 6-2) for a list of procedures required at this visit. Other assessments should be performed as clinically indicated.

6.6. Renal Biopsies

The local biopsy reports will be used for the purposes of randomization. A tissue sample from the renal biopsy used to qualify the subject for randomization needs to be sent to a central reading center after Day 0 (baseline). Tissue from any renal biopsies performed as part of routine care anytime after baseline (Day 0) will also be collected, where possible, for a similar central reading.

6.7. Laboratory Tests

Non-fasting clinical laboratory tests will be performed as outlined in the Study Calendar (see Table 6-1, Table 6-2, and Table 6-3).

Due to the potential for unblinding, the following lab results will not be provided to study sites after baseline (Day 0): aCL (IgM, IgG, IgA isotypes), ANA, anti-Sm, anti-C1q, serum immunoglobulin isotypes IgM/IgA, and the results from the biological markers measured by FACS analysis listed below.

In geographies where feasible, the following biological markers will be measured (using FACS analysis):

- Peripheral B lymphocytes:
  $CD20^{+}$, $CD20^{+}/27^{+}$ memory, $CD20^{+}/27^{-}$ naïve, $CD20^{+}/69^{+}$ activated, $CD20^{+}/138^{+}$ plasmacytoid, $CD19^{+}/27^{BRIGHT}/38^{BRIGHT}$ SLE subset, $CD19^{+}/CD24^{HIGH}/CD38^{HIGH}$ regulatory B cells, and $CD20^{-}/138^{+}$ plasma cells.

For the renal function assessments at all study visits, the simplified MDRD formula (below) will be used to estimate GFR (Levey et al, 2006):

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

The serum creatinine concentration is expressed in mg/dL.

In addition, at Baseline (Day 0), Week 24, 48, 52, 76, 100, and 104, the glomerular filtration rate (GFR) will be calculated based on creatinine clearance determined from the mean creatinine value of 2 contiguous 24 hour urine collections and 2 serum creatinine measurements (first serum creatinine collected at initial visit and the second sample taken 3 days later at the follow-up visit). Subjects will be provided with the materials for collecting the two 24 hour urine collections beginning the next morning following their initial clinic visit. On the third day following the initial visit, subjects will return to the clinic for the second serum creatinine sample.

It has been demonstrated that there is a strong correlation between the protein content of a 24-hour urine collection and the urinary protein: urinary creatinine ratio in a single urine sample (Ginsberg et al, 1983; Ruggenenti et al, 1998; KDOQI Clinical Practice Guidelines for Chronic Kidney Disease 2002; Price et al, 2005). Given this information, spot urinary protein: urinary creatinine ratio will be used for determining proteinuria in this study for renal response assessments and the SELENA SLEDAI (Appendix 3) disease activity indices.

For the urinary sediment assessments, both menstrual cycles and genitourinary tract infections may be confounders. The urine collection may be postponed up to 14 days at the investigators discretion if menstrual bleeding or a genitourinary tract infection is present at anytime during the 24 hour urine collection.

An exploratory analysis of urinary biomarkers related to lupus nephritis may be performed at baseline (pre-dose) and at selected timepoints thereafter. Data collection and analysis will be performed independently of the main study and will form the basis of a separate report. The biomarkers include, but are not limited to, MCP-1, hepcidin, NGAL, LFABP, Angiogenin, Angiopoietin 2, Angiostatin, IL-6r, Osteopontin, PAI-1, PF4, RAGE, RANK, Sgp130, Siglec 5, Siglec 9, Tgf-beta1, TIM1, TIMP-2, TLSP, TNFR-II, Trem1, VCAM-1, Vegf-C, and VEGF-R3.

Additional instructions regarding collection procedures are provided in the Study Procedures Manual and Central Laboratory Manual.

6.7.1. Pharmacokinetics

All randomized subjects will be sampled for serum belimumab levels. A blood sample for pharmacokinetic analysis will be drawn according to the time schedule below.

Table 6-4 PK Visit Days and Sample Times

Day (Week)	Time (Related to Dosing of Study Agent)
Day 0	Before the start of infusion
Day 3	Anytime during visit
Day 14 (Week 2)	Prior to dosing, 0 - 4 hours after the end of infusion
Day 28 (Week 4)	Prior to dosing, 0 - 4 hours after the end of infusion
Day 56 (Week 8)	Prior to dosing
Day 168 (Week 24)	Prior to dosing, 0 - 4 hours after the end of infusion
Day 171 (Week 24 + 3 days)	Anytime during visit
Day 364 (Week 52)	Prior to dosing
Day 728/Exit (Week 104)	Anytime during visit (or prior to dosing if going into the open-label treatment period of the study)
8-week follow-up	Any time during visit
Open Label 8-week follow-up	Any time during visit

On days study agent is administered and blood samples for pharmacokinetic analysis are obtained after infusion, blood samples for pharmacokinetic analysis should not be taken from the same arm used for the administration of study agent. Samples may be obtained by venipuncture.

If a subject withdraws from treatment with study agent, a blood sample for pharmacokinetic analysis will be drawn any time during visit at 4 weeks and 8 weeks after the last dose of study agent is administered. If a subject withdraws consent from the study, an attempt should be made to obtain a blood sample for pharmacokinetic analysis at the follow-up visits approximately 4 and 8 weeks after the last dose of study agent.

Detailed instructions regarding the collection, processing, storage and shipment of blood samples are available in the Study Procedures Manual that is provided to all study sites**.**

6.7.2. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology in alignment with the FDA premarketing clinical liver safety guidance [James, 2009; Le Gal, 2005].

Liver Chemistry Stopping Criteria- Liver Stopping Event	
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

1) Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject 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 subjects 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).

6.7.2.1. Required Actions and Follow up Assessments following ANY Liver Stopping Event

ACTIONS:

- Immediately discontinue study treatment
- Report the event to GSK **within 24 hours**
- Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE (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 subjects receiving anticoagulants)
- Perform liver event follow up assessments
- Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below)

Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 10).

MONITORING

For bilirubin or INR criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours**
- Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline
- A specialist or hepatology consultation is recommended

For All other criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours**
- Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline

FOLLOW UP ASSESSMENTS

- Viral hepatitis serology (includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM) and HBV DNA (see Section 6.7.5); 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)
- Blood sample for pharmacokinetic (PK) analysis, obtained within approximately one to two weeks after last dose (PK sample may not be required for subjects 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 blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject'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 SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total 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

For bilirubin or INR criteria:

- 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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects 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.

6.7.3. Increased Monitoring Criteria with Continued Therapy

If met see required actions below:

- If 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

6.7.3.1. Required Actions and Follow Up Assessments for Increased Monitoring with Continued Therapy

- Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety.
- Subject can continue study treatment
- Subject 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 subject meets the liver chemistry stopping criteria, proceed as described above for Required Actions and Follow up Assessments following ANY Liver Stopping Event
- 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 subjects twice monthly until liver chemistries normalize or return to within baseline.

6.7.4. Study Treatment Restart

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than drug induced liver injury [DILI]) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity.

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).
- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, or possible study treatment-induced liver injury) are reviewed and excluded
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.

- If restart of study treatment is approved by GSK Medical Governance in writing, the subject 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 subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section 7.2.

6.7.5. Additional Hepatitis B Monitoring

Safety assessment for Hepatitis B during the trial will be as follows:

- ALT and/or AST elevations of greater than 2.5 x ULN will require:
- Sites to review laboratory results for anti-HBc from Screening visit:
  - If Screening anti-HBc result was reactive, then obtain HBV DNA.
  - If HBV DNA returns reactive, withdraw subject from further treatment and enter follow up visit schedule. Investigator will determine the extent of required attention for proper follow up of potential hepatitis B re-activation.
  - If anti-HBc result from Screening visit was negative, then repeating hepatitis B testing is optional per investigator upon investigating for other causes.
- Refer to the SPM for guidance on documenting the suspected reason for ALT and/or AST elevations of greater than 2.5 x ULN.

6.7.6. Immunogenicity

Serum samples for anti-belimumab antibody measurements will be obtained from all randomized subjects before administration of study agent at baseline (Day 0), and at any time on Week 8, Week 24, Week 52, Week 76 and Week 104 in the double-blind portion of the study. During the open-label extension, a sample will be collected at Week 24. Additionally, a sample will be collected at the 8-week follow-up visit.

6.8. Withdrawal of Subjects from Treatment

In addition to the reasons for withdrawal detailed below, subjects are free to withdraw from treatment or from the study at any time, for any reason, or may be withdrawn/removed, if necessary, to protect their health. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided. Subjects who withdraw from treatment/study after receiving at least 1 dose of study agent will not be replaced.

Subjects should be withdrawn from treatment with study agent for any of the following reasons:

- Missing 3 or more consecutive doses of study agent
- Prohibited concurrent medication or prohibited dose of concurrent medication (see Section 5.5 and Section 5.6).
- Prohibited therapy.
- Unacceptable toxicity (see Section 5.4).
- Pregnancy.
- Withdrawal of consent (including use and disclosure of research-related health information).
- Subjects positive for Anti-HBc at Screening who develop elevated LFTs >2.5 x ULN during the study followed by an HBV DNA test that shows detectable viral load (see Section 6.7.5).

All subjects who discontinue treatment with study agent during the double-blind period (for reasons other than withdrawal of consent) should return for all scheduled visits through Week 104.

In the event that a subject withdraws consent during the double-blind period, an attempt should be made to obtain consent to collect follow-up safety data (at an exit visit approximately 4 weeks after the last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent) and to obtain survival status at Week 104. Any subject that withdraws consent for use and disclosure of research-related health information will be considered withdrawn from the study and will not be followed for mortality.

All subjects who discontinue treatment during the open-label extension should return for an Exit visit (4 weeks after the last dose of study agent) and a follow up visit 8 weeks after the last dose of study agent. The follow-up visit is not required for subjects entering the separate continuation protocol.

6.9. Subject Unblinding

Belimumab and placebo will be supplied as open-label vials and 3rd party unblinding will be employed. The study agent will be reconstituted and diluted by the unblinded site pharmacist or qualified designee, independent of the study (person responsible for

receiving and dispensing study agent). Except for a limited number of safety oversight personnel, all study site personnel, the subject, the sponsor, and the Contract Research Organization (CRO) will remain blinded to the study agent received and to the results of certain biomarker and pharmacodynamic laboratory results (see Section 6.7). Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

In the case of a medical emergency when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject, the study blind may be broken for the specific subject. Whenever possible, the investigator should discuss options with the Medical Monitor prior to unblinding any subject. If this is impractical, the investigator must notify the Medical Monitor as soon as possible of any broken blind, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. Any broken blind will be clearly justified and explained by a comment in the eCRF.

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

7. ADVERSE EVENT REPORTING

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.1. Definitions

ADVERSE EVENT Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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 medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- 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 prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This 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. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where 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
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

SERIOUS ADVERSE EVENT: A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 hospitalisation or prolongation of existing hospitalisation

   NOTE: In general, hospitalisation signifies that the subject 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 out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

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

d. Results in disability/incapacity, or

   NOTE: 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 or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are 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 hospitalisation, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

   NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

7.2. Reporting Adverse Events to the Sponsor

All adverse events (AEs) that are identified from the start of study agent administration (Day 0) through 8 weeks following administration of the last dose of study agent will be recorded on the Adverse Event Case Report Form (AE eCRF). All data fields on the AE eCRF must be completed.

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

Serious Adverse Events (SAEs) must be recorded on the SAE eCRF within 24 hours of site personnel becoming aware of the SAE, regardless of expectedness. All fields of the SAE eCRF should be completed, but completion of the report should not be held until all information is available. Follow-up information and corrections should be added to the SAE eCRF within 24 hours of site personnel becoming aware of the event as described in the Study Procedures Manual.

In addition, prior to study drug administration, any SAE assessed **as related** to study participation (eg, protocol mandated procedures, invasive tests) will be reported as an SAE from the time a subject consents to participate in the study.

For subjects in China, prior to study drug administration, SAE(s) regardless of relationship to study participation (eg, protocol mandated procedures, invasive tests) or study treatment will be reported from the time a subject consents to participate in the study.

SAEs that occur off study, after the follow-up period, that are assessed by the investigator as being definitely, possibly or probably related to study agent must be reported to the Sponsor as outlined in the Study Procedures Manual.

7.3. Other Events Requiring Rapid Reporting (Protocol Specified Events)

Protocol Specified Events (PSEs) are additional events that must be reported in an expedited manner. A PSE may or may not be an SAE. PSEs are considered SAEs if they meet 1 or more of the criteria for an SAE (see Section 7.1). PSEs are recorded on the PSE page of the eCRF within 24 hours of site personnel becoming aware of the event.

IgG < 250 mg/dL (Grade 4) is a protocol specified event for this protocol.

7.4. Laboratory Abnormalities as Adverse Events

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine RBC increased). In addition, an IgG abnormality < 250 mg/dL (Grade 4) should always be recorded on the PSE page of the eCRF. IgG < 250 mg/dl should also be reported as an SAE if it meets one or more of the SAE criteria in Section 7.1.

Laboratory tests are graded according to the Adverse Event Severity Grading Tables in Appendix 7. If a particular lab test is not listed in Appendix 7, the lab test should be graded as mild, moderate, or severe as specified in Section 7.8.

7.5. Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant

pharmacotherapy, including belimumab. 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 immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

7.6. Suicidality Assessment

Some autoimmune diseases have an increased risk of suicidal behaviour and/or ideation (Bachen et al, 2009; Timonen et al, 2003; Stenager et al, 1992). In order to objectively assess suicidality in belimumab clinical programs the C-SSRS (Appendix 8 and Appendix 9) will be utilized to collect information on suicidal behavior and ideation. SLE patients have an increased prevalence of mood and anxiety disorders compared with the general population and disease activity may contribute to this higher risk. The incidence of major depressive disorder (MDD) among SLE patients has been reported to be as high as 47% (Bachen et al, 2009). Since active SLE and MDD may increase the risk of suicidal ideation or behavior before or during clinical studies, subjects participating in the double-blind portion of this study will be assessed for suicidality at every visit.

Subjects who answer "yes" to any suicidal behavior or "yes" to suicidal ideation questions 4 or 5 on the C-SSRS should be referred to appropriate psychiatric care and prompts the completion of an SAE worksheet. The Medical Monitor should be notified when these events occur. In addition, a "yes" to any suicidal behavior or "yes" to suicidal ideation question 3, 4 or 5 on the C-SSRS prompts the completion of the Possible Suicidality Related History Questionnaire (PSRHQ, only the first time this condition is met; refer to Appendix 11 for the PSRHQ) eCRF and a Possible Suicidality Related Questionnaire (PSRQ) eCRF (at all times this condition is met; refer to Appendix 12 for the PSRQ).

Baseline/Screening and during treatment assessment of suicidality will be performed during the blinded portion of this study using C-SSRS (refer to Appendix 8 and Appendix 9 for C-SSRS). The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both behaviour and ideation (Posner et al, 2007). The C-SSRS is administered by a qualified clinician and is designed to address the need for a summary measure to track change in the severity/density of suicidality across both clinical settings and treatment trials. It assesses intensity of ideation (a potentially important marker of severity) by specifically asking about frequency, duration, intrusiveness, controllability, and deterrents. In addition, it captures both the modal and most severe forms of ideation. The C-SSRS is to be completed by the investigator or his/her qualified designee at every visit during the double-blind portion of the study.

Although assessment of suicidality using the C-SSRS will take place only during the blinded portion of the study, investigators are reminded of the importance to clinically

assess for suicidality at every visit given that SLE patients are at increased risk of suicidal behavior and/or ideation.

7.6.1. Possible Suicidality Related Questionnaire (PSRQ)

The investigator will be prompted to complete the PSRQ (in addition to the AE, SAE pages, and PSRHQ as appropriate) if a "yes" response is given to any suicidal behaviour or a "yes" response to suicidal ideation questions 3, 4 or 5 on the C-SSRS. Refer to Appendix 12 for the PSRQ. If the adverse event meets the definition of an SAE, which includes a "yes" answer to any suicidal behaviour or a "yes" to suicidal ideation questions 4 or 5 on the C-SSRS, the site must ensure that there are no significant discrepancies between the PSRQ and SAE.

7.7. Reporting a Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to the Sponsor within 24 hours of learning of its occurrence. All pregnancies that are identified from the start of study agent through 16 weeks following the last dose of study agent should be reported. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to the Sponsor.

7.8. Investigator Evaluation of Adverse Events

The investigator will evaluate all adverse events with respect to seriousness (criteria for seriousness are listed in Section 7.1), severity (intensity), and causality (relationship to study agent). The investigator will make an assessment of intensity based on the Division of Microbiology and Infectious Diseases (DMID) Adverse Event Severity Grading Tables (see Appendix 7) where possible:

SEVERITY:

- **Mild** An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities (Grade 1 DMID).
- **Moderate** An event that is sufficiently discomforting to interfere with everyday activities (Grade 2 DMID).
- **Severe** An event that prevents normal everyday activities (Grade 3 or 4 DMID).
- **Not applicable** Those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

CAUSALITY:

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of 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 when 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 prior to the initial transmission of the SAE data to GSK.** The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.9. Follow-up of Adverse Events

Serious and non-serious adverse events that occur from the start of study agent administration through 8 weeks after the date of last administration of study agent are reported. In addition, prior to study drug administration, any SAE assessed **as related** to study participation (eg, protocol mandated procedures, invasive tests) will be reported as an SAE from the time a subject consents to participate in the study For subjects in China, prior to study drug administration, SAE(s) regardless of relationship to study

participation (eg, protocol mandated procedures, invasive tests) or study treatment will be reported from the time a subject consents to participate in the study. For subjects who discontinue treatment with study agent during the double-blind period (for reasons other than withdrawal of consent), all SAEs, regardless of relationship to study drug, will be collected through Week 104.

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (see Section 8.6.2) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. This applies to all subjects, including those withdrawn prematurely.

PSEs (see Section 7.3) that occur after Screening visit through 8 weeks after the date of last administration of study agent are reported and followed as described above for AEs/SAEs.

7.10. Disease Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) (preferred terms; MedDRA v. 14.0) are common in subjects with SLE and can be serious/life-threatening:

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

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to the Sponsor (even though the event may meet the definition of a serious adverse event). These events will be recorded on the DRE page in the subject's eCRF. ***However, if one or both of the following conditions apply, then the event should be reported as an SAE using the standard process:***

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject, or
- The Investigator considers that there is a reasonable possibility that the event was related to treatment with the study agent

If either of the above conditions is met then record the DRE on the SAE page rather than the DRE page and report promptly (i.e., expedited reporting, see Section 7.2) to the Sponsor.

7.11. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to the Sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and the Sponsor's policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8. ENDPOINTS AND STATISTICAL ANALYSIS

8.1. General Statistical Considerations

Unless otherwise specified, all analyses will be performed on the intention to treat (ITT) population defined as all subjects who are randomized and receive at least 1 dose of study agent. The ITT analysis will be performed according to the treatment that a subject was randomized to receive, regardless of the actual treatment received.

The database will be locked for the primary analysis after data through the Week 104 visit for all subjects have been collected, verified and validated. All subjects and study site personnel will remain blinded until the final database lock, which will occur after data have been collected, verified and validated for all subjects completing the 8 week follow-up after the open-label extension.

For the analysis of the primary and the major secondary efficacy endpoints, a step-down sequential testing procedure will be used to control the overall type 1 error. With this procedure, the primary and 4 major secondary efficacy endpoints will be evaluated for statistical significance based on a pre-specified sequence for interpretation: (1) primary efficacy renal response (PERR) at Week 104, (2) complete renal response (CRR) at Week 104, (3) PERR at Week 52, (4) time to death or renal-related event, and (5) ordinal renal response (ORR) at Week 104. 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, although nominal p-values may be reported and considered descriptive.

Analyses of other efficacy endpoints other than the major secondary efficacy endpoints will not be subject to any multiple testing procedure. All statistical tests will be 2-sided and performed at an overall significance level of 0.05.

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

8.2. Randomization Procedure and Assignment to Treatment Groups

This is a Phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled study. Once subjects have consented, have undergone all screening procedures and have been determined to be eligible for the study, they will return for the baseline (Day 0) visit to be randomized in a 1:1 ratio (via an Interactive Web Response System) to 1 of 2 treatment groups (10 mg/kg belimumab plus standard of care or placebo control plus standard of care. The randomization of all eligible subjects will be stratified by their induction regimen (HDCS plus CYC vs HDCS plus MMF) and race (black race vs other).

8.3. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will review unblinded safety data for this Phase 3 program on an ongoing basis until the data are locked and analyzed through Week 104 (after which monitoring may be assumed by an internal GSK/HGS committee). The IDMC will include physicians with expertise in infectious disease, rheumatology or nephrology and a statistician, none of whom are affiliated with the sponsor. The first review will occur 6 months after the first subject is randomized or after the first 20 subjects are randomized and have completed a Week 8 visit, whichever is sooner. Thereafter, the IDMC will review the data approximately every 6 months. At all times the sites and sponsor will remain blinded to treatment allocation. Events to be monitored during the safety review will include, at a minimum, all serious adverse events (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 and open-label extension portions of the study. Investigators (and IRBs/IECs, as appropriate,) will be notified of the outcome of each IDMC meeting.

The IDMC will receive information within 72 hours of the sponsor or designee receiving notification of all SAEs that are life threatening or result in death. Other SAEs will be provided to the IDMC within 15 calendar days. In addition, the IDMC will receive information on all serious infections and all opportunistic infections, irrespective of relationship to study agent, within 15 calendar days.

8.4. Sample Size Rationale

The sample size was calculated using the ORR as the primary endpoint and assuming the endpoint proportions of complete, partial, and no renal response will be 25%, 25%, and 50%, respectively, for subjects on placebo plus standard of care (Appel et al, 2009; Sinclair et al, 2007; Dooley et al, 2011) and 32.5%, 32.5%, and 35%, respectively, for subjects on belimumab plus standard of care. Using these assumptions, simulations were performed using Van Elteren methods at the 5% significance level and a 1:1 randomization allocation ratio, a target sample size of N=464 subjects is required (232 per arm) to achieve at least 85% power to detect a treatment difference for the primary endpoint.

In the event of recruitment challenges, randomization may be stopped as long as the number randomized is ≥400 subjects. The table below provides power estimates for sample sizes from 400 to 464 based on the original ORR assumptions.

Sample Size Total	Sample Size Per Arm	Power
400	200	80.13%
420	210	81.43%
440	220	83.40%
460	230	84.62%
464	232	85.60%

Assuming placebo response rates of 25%/25%/50%, the smallest response rates on belimumab resulting in a statistically significant difference range from 30.3%/30.3%/39.4% (for N=400) to 30.0%/30.0%/40.0% (for N=464).

8.4.1. Power for PERR Endpoint

PERR response rates are based on our assumptions for the Placebo+SOC responses assumed in the original ordinal endpoint (25% complete response and 25% partial response). Given the PERR endpoint is more stringent than a partial response but less stringent than the complete response, if one assumes a portion of the partial responders would meet the PERR criteria, then an expected response rate of approximately 40% for the Placebo+SOC arm is a reasonable estimate. Due to the lack of published data on the endpoint, there is a degree of uncertainty regarding the response rates; therefore a range of possible response rates and the associated power is provided.

For the new primary endpoint, PERR (Responder vs. Non-Responder), and the final sample size of N=448, there is 80% power to detect a 13.6% treatment difference and a minimum detectable difference of 9.7% for response rates spanning the 50% mark (40% vs. 53.6%) of the binomial distribution, the area of maximum variance. Given the achieved sample size of N=448, the table below provides the treatment difference required to achieve 80% power based on placebo response rates ranging from 20% to 50% in 5% increments.

Placebo (Pbo) %Response	Belimumab (Bel) %Response	Treatment Difference (Bel – Pbo)	Minimum Detectable Difference
20	32.0	12.0	8.4
25	37.7	12.7	8.9
30	43.2	13.2	9.3
35	48.5	13.5	9.5
40	53.6	13.6	9.7
45	58.6	13.6	9.7
50	63.5	13.5	9.7

Based on methods for Fisher's Exact Test using PASS 12.0 software.

8.5. Efficacy

8.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is Primary Efficacy Renal Response (PERR) at Week 104, as follows:

- Responder: Defined by a response at the Week 100 visit confirmed by a repeat measurement at the Week 104 visit, as follows:

  Estimated glomerular filtration rate (GFR) is no more than 20% below the pre-flare value or $\geq$ 60 mL/min/1.73m^2

  AND

  Urinary protein:creatinine ratio $\leq$ 0.7

  AND

  No receipt of prohibited (rescue) therapy resulting in treatment failure (see Section 5.5 and Section 5.6).

- Non-responder: Not meeting criteria for the PERR.

The PERR at the Week 104 visit will be derived as below:

At Week 100	At Week 104	PERR at Week 104
Responder	Responder	Responder
Responder	Non-Responder	Non-Responder
Non-Responder	Responder	Non-Responder

PERR at the Week 52 visit will be derived using a similar approach to that described above for the Week 104 visit, but using the Week 48 and Week 52 visits.

8.5.2. Primary Efficacy Analyses

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

Subjects who discontinue study agent should remain on study and undergo protocol required assessments through Week 104. Subjects who are withdrawn from the study agent prior to Week 104 will be imputed as a non-responder.

8.5.2.1. Missing Values

The following imputation method will be used to handle a missing visit related to the primary endpoint assessment:

- If the Week 104 visit is missing, the primary endpoint will be determined using data from the Week 96 and the Week 100 visits.
- If the Week 100 visit is missing, the primary endpoint will be determined using data from the Week 96 and the Week 104 visits.
- If a subject misses both the Week 100 and the Week 104 visit, the subject will be defined as a non-responder.

If only 1 laboratory component of the renal response endpoint is missing at only 1 visit, the following imputation method will be used for subjects missing a component of the primary endpoint:

- If this component is missing at the Week 104 visit, the missing component will be determined using data on the component from the Week 96 and the Week 100 visits.
- If this component is missing at the Week 100 visit, the missing component will be determined using data on the component from the Week 96 and the Week 104 visits.
- If this component is missing at both the Week 100 and the Week 104 the subject will be defined as a non-responder.

The parallel approach will be taken at Week 52 with the exception of the case with missing components at Week 48 and Week 52, in which case the subject will be defined as a non-responder.

8.5.2.2. Sensitivity Analyses

The robustness of the primary efficacy results will be assessed by comparing PERR at the Week 104 visit between treatment groups in the completer population. The completer population is defined as all subjects who completed through Week 104 and were not permanently discontinued from treatment prior to Week 104. The analysis will be performed using the same method as the primary endpoint analysis.

Other sensitivity analyses will be specified in the statistical analysis plan.

8.5.2.3. Subgroup Analysis

Subgroup analysis of the primary efficacy endpoint (ie, PERR at Week 104) will be performed in the following subgroups:

- Induction regimen (HDCS plus CYC vs HDCS plus MMF).
- Race (Black vs Non-Black).
- Region (US/Canada, Europe/Australia/Israel, Asia, Americas excluding US and Canada).
- Baseline anti-dsDNA (anti-dsDNA ≥ 30 IU/mL vs other).
- Baseline complement (C3 and/or C4 low vs other).
- Baseline complement and anti-dsDNA (C3 and/or C4 low AND anti-dsDNA ≥ 30 IU/mL vs other).
- Baseline Renal Biopsy Class (Class III or Class IV Only; Class V Only; Class V plus Class III or Class IV; Other).

8.5.3. Secondary Efficacy Endpoints

8.5.3.1. Major Secondary Efficacy Endpoints

- Complete renal response (CRR) at Week 104 (see definition under ORR).
- PERR at Week 52.
- Time to death or renal-related event defined as any of the following: i) end stage renal disease (ESRD), ii) doubling of serum creatinine, iii) renal worsening as evidenced by increased proteinuria and/or impaired renal function, or iv) renal disease-related treatment failure. Further definition details will be provided in the analysis plan.
- ORR (complete, partial or no response) at Week 104 defined as follows:
  - CRR:

    Estimated glomerular filtration rate (GFR) is no more than 10% below the pre-flare value or within normal range

    AND

    Urinary protein:creatinine ratio < 0.5

    AND

    No receipt of prohibited (rescue) therapy resulting in treatment failure (see Section 5.5 and Section 5.6).

  - Partial Renal Response (PRR):

    Estimated GFR no more than 10% below the baseline value or within normal range

    AND

≥ 50% decrease in the urine protein:creatinine ratio with one of the following:

- a urine protein:creatinine ratio of < 1.0, if the baseline ratio was ≤ 3.0
  OR
- a urine protein:creatinine ratio of < 3.0, if the baseline ratio was > 3.0

AND

- No receipt of prohibited (rescue) therapy resulting in treatment failure (see Section 5.5 and Section 5.6).

- No Renal Response (NRR):

  Not meeting criteria for either CRR or PRR.

8.5.4. Other Efficacy Endpoints

Disease activity

- Change from baseline in SELENA SLEDAI score by visit.
- Proportion of subjects with SELENA SLEDAI score < 4 by visit.
- Proportion of subjects with improvement in SELENA SLEDAI organ systems from baseline by visit.
- Proportion of subjects with worsening in SELENA SLEDAI organ systems from baseline by visit
- Change from baseline in SELENA SLEDAI excluding renal items by visit.

Note: Programmed analysis of these endpoints will apply SLEDAI-S2K proteinuria scoring.

Flares*

- Time to first severe SFI flare.
- Time to first severe SFI flare after Week 24.

*Severe SFI flare will be defined by using the modified SLE Flare Index (SFI) and will be described in the statistical analysis plan.

Renal Specific Measures

- Individual components of PERR. Proportion of subjects with the following by visit:
  - Urinary protein:creatinine ratio ≤ 0.7.
  - Estimated GFR no more than 20% below the pre-flare value or ≥ 60 mL/min/1.73m^2.
  - No receipt of prohibited (rescue) therapy resulting in treatment failure (see Section 5.5 and Section 5.6).

- Individual components of CRR. Proportion of subjects with the following by visit:
  - Urinary protein:creatinine ratio < 0.5.
  - Estimated GFR no more than 10% below the pre-flare value or within the normal range
- Percent change in proteinuria by visit.
- Change in proteinuria by visit.
- Proportion of subjects with a doubling of the serum creatinine or progression to end stage renal disease (ESRD) as defined below:
  - Doubling of serum creatinine compared with baseline that is confirmed with a second measurement at least 3 weeks later.
  - Progression to ESRD defined as the need for chronic dialysis or renal transplantation.
- Time to first PERR that is maintained through Week 52.
- Time to the first PERR that is maintained through Week 104.
- Time to the first CRR that is maintained through Week 52.
- Time to the first CRR that is maintained through Week 104.
- Proportion of subjects with PERR by visit.
- Proportion of subjects with CRR by visit.

Corticosteroid Use

- Proportion of subjects receiving ≤ 5 mg/day prednisone by visit.
- Proportion of subjects receiving ≤ 7.5 mg/day prednisone by visit.

SLICC Damage Index (SDI)

- SDI change from baseline at Week 104
- Percent of patients with any SDI worsening (change >0) at Week 104 compared with baseline.

Biomarkers

1. Median/mean percent change and median/mean absolute change from baseline in absolute B cell subsets ($CD20^+$, $CD20^+/27^+$ memory, $CD20^+/27^-$ naïve, $CD20^+/69^+$ activated, $CD20^+/138^+$ plasmacytoid, $CD19^+/27^{BRIGHT}/38^{BRIGHT}$ SLE subset, $CD19^+/CD24^{HIGH}/CD38^{HIGH}$ regulatory B cell, and $CD20^-/138^+$ plasma cells) by visit. Only in regions/countries where assessment of B cells is feasible.
2. Median/mean percent change and median/mean absolute change from baseline by visit
   - Total serum immunoglobulin (IgG and other isotypes: IgM and IgA).
   - Autoantibodies* (anti-dsDNA, ANA, aCL, anti-Sm, and anti-C1q).
   - Complement (C3, C4) levels.

3. Percent of patients with normalized serological activity at Week 104 and over time
   - IgG, IgM and IgA (high to normal/low).
   - Autoantibodies* (anti-dsDNA, ANA, aCL, anti-Sm, and anti-C1q) present to absent.
   - Complement (C3, C4, and C3 AND C4) levels low to normal/high.

* Anti-dsDNA will be collected monthly throughout the double-blind treatment period. Other autoantibodies will be collected from all patients at baseline, then at regular intervals during the study.

Data collection and analysis of the exploratory renal biomarkers will be performed independently of the main study and will form the basis of a separate report.

8.5.5. Secondary Efficacy Analyses

8.5.5.1. Major Secondary Efficacy Analyses

Time to death or renal-related event will be compared between belimumab vs. placebo using a Cox proportional hazards model controlling for induction regimen (CYC vs. MMF), race (Black vs. Non-Black) baseline proteinuria, and baseline eGFR.

CRR at Week 104 and PERR at Week 52 will be compared between belimumab and placebo using logistic regression controlling for induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline proteinuria, and baseline eGFR.

Analysis of ORR (complete, partial or no response) at Week 104 will be compared between belimumab vs. placebo using rank analysis of covariance (ANCOVA) controlling for induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline proteinuria, and baseline eGFR.

8.5.6. Other Efficacy Analyses

The analysis of all other efficacy endpoints will be described in the statistical analysis plan.

8.6. Safety

8.6.1. Definition of Safety Variables

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

8.6.2. Analysis of Safety Variables

AEs will be graded for severity by the investigator using Adverse Event Severity Grading Tables (Appendix 7) or the grades in Section 7.8, as appropriate. The frequency and incidence of AEs will be tabulated by MedDRA system organ class (SOC) and preferred

term. Additional analysis may be performed based on event rates adjusting for subject-years on study agent if the dropout rates are unbalanced across treatment groups. AEs will also be summarized by MedDRA SOC and preferred terms for those that are considered to be severe (Grade 3 and Grade 4) and those that are considered serious. Discontinuations due to AEs will be summarized.

The frequency and incidence of laboratory abnormalities will be tabulated by treatment group. Laboratory values will be assessed for significant changes from baseline. Laboratory toxicity will be graded using Adverse Event Severity Grading Tables (Appendix 7) when possible. Shift tables will be used to determine if subjects move from normal to abnormal during the course of the study. Shifts of ≥ 2 grades and Grade 3 or 4 laboratory abnormalities will be summarized.

Safety Endpoints of Special Interest

- All cause mortality
- Serious and/or severe infections
- Opportunistic infections
- Malignant neoplasms
- Selected serious psychiatric events
- Suicidality assessment (see Appendix 8 and Appendix 9)
- Hypersensitivity reactions/anaphylaxis
- Immunogenicity

The analyses of these safety endpoints will be described in the statistical analysis plan.

8.7. Pharmacokinetics

8.7.1. Definition of Pharmacokinetic Evaluation

All randomized subjects will be sampled for serum belimumab levels. Serum belimumab concentration data will be used in a population PK analysis. Assessment of belimumab concentrations will be performed at the timepoints indicated in Section 6.7.1.

8.7.2. Analysis of Pharmacokinetics

Serum belimumab concentration will be determined by an electrochemiluminescence (ECL)-based assay. Results for this study will be presented using appropriate graphic and tabular summaries. Serum belimumab concentration data obtained from this study will be used in a population PK analysis, which will be reported separately. Potential effects of demographic and disease characteristics, concurrent medications or renal function on belimumab PK will be evaluated.

9. PHARMACOGENETICS (PGX)

In consenting subjects, a blood sample for PGx research should be drawn predose at baseline (Day 0) to better characterize genetic variability (eg, HLA typing) that may affect efficacy or safety endpoints. Information regarding PGx research is included in Appendix 6.

The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the study site. The approval(s) must be in writing and clearly specify approval of the PGx assessments (ie, approval of Appendix 6). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate that approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments are not approved, then approval for the rest of the study will clearly indicate this and that PGx assessments will not be conducted.

10. STUDY ADMINISTRATION

Belimumab is under development by GlaxoSmithKline Pharmaceuticals. Human Genome Sciences, Inc. a wholly owned subsidiary of GlaxoSmithKline Pharmaceuticals is the sponsor of this study.

10.1. Informed Consent

A copy of the proposed informed consent document must be submitted to the sponsor or designee for review and comment prior to submission to the reviewing IRB/IEC. The consent form must be approved by the IRB/IEC and contain all elements required by national, state, local, and institutional regulations or requirements.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information using the IRB/IEC approved informed consent document(s), including the objective and procedures of the study and the possible risks involved before inclusion in the study. Each subject must voluntarily provide written informed consent (including consent for the use and disclosure of research-related health information). The consent must be obtained prior to performing any study-related procedures that are not part of normal patient care, including screening and changes in medications including any washout of medications. A copy of the signed informed consent must be given to the study subject.

10.2. Institutional Review Board Review/Independent Ethics Committee Review and Approval

The investigator or sponsor (as appropriate per national regulations) shall assure that an IRB/IEC, constituted in accordance with the ICH Guideline for Good Clinical Practice (GCP), will provide initial and continuing review of the study.

Prior to shipment of the study agent and enrollment of study subjects, documented IRB/IEC approval of the protocol, informed consent form, and any advertisement for subject recruitment must be obtained and provided to the sponsor or designee.

The IRB/IEC must also be informed of all protocol amendments prior to implementation. The investigator must provide reports of any change in research activity (ie, the completion, termination, or discontinuation of a study) to the IRB/IEC.

10.3. Protocol Compliance

Except for a change that is intended to eliminate an apparent immediate hazard to a study subject, the protocol shall be conducted as described. Any such change must be reported immediately to the sponsor and to the IRB/IEC.

10.4. Protocol Revisions

Protocol amendments will be prepared and approved by the sponsor. All protocol amendments will be signed by the investigator and submitted to the IRB/IEC for review prior to implementation. Documentation of IRB/IEC approval must be forwarded to the sponsor or designee. If an amendment significantly alters the study design, increases potential risk to the subject or otherwise affects statements in the informed consent form, the informed consent form must be revised accordingly and submitted to the IRB/IEC for review and approval. The approved consent form must be used to obtain informed consent from new subjects prior to enrollment and must be used to obtain informed consent from subjects already enrolled if they are affected by the amendment.

10.5. Data Collection and Management

The investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. The investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs, or tapes.

The anonymity of participating subjects must be maintained. For data collection and management purposes, subjects are to be identified by a subject number only. Documents that identify the subject beyond subject number will not be submitted to the sponsor (eg, the signed informed consent document; subject initials) and must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

Site personnel record all data for each study subject through electronic case report forms (eCRFs) using an Electronic Data Capture (EDC) system provided and approved by the sponsor. Refer to the Study Procedures Manual for additional information regarding CRFs that will be used as source documentation. Sites must complete the eCRFs in a timely manner and the investigator must promptly review the completed eCRFs after every visit for each subject. As the person ultimately responsible for the accuracy of all eCRF data, the investigator must sign the Investigator's Statement in each subject's eCRF.

The EDC system automatically generates queries resulting from the computer checks embedded into the system, so as to ensure accuracy, quality, consistency, and completeness of the database. Manual queries resulting from review by monitors, medical coders, and other Data Management staff are also generated from within the EDC system, where they are tracked. Sites resolve the queries and correct the entered data when necessary. Every change to data is captured in the EDC system audit trail. Upon completion of the study, or after reaching a pre-specified point in the study, Data Management will lock the database and generate the SAS datasets necessary for data analysis and reporting. Upon completion of the study, each site will be provided with a compact disc (CD) containing the eCRFs for each of their subjects.

10.6. Study Monitoring

The study sponsor or designee will monitor the study. Study monitors representing the sponsor will visit study sites routinely throughout the trial. The sponsor will review eCRFs and compare them with source documents to verify accurate and complete collection of data and confirm that the study is being conducted according to the protocol. Auditors representing the sponsor may also similarly evaluate the study and its monitors. For these purposes, the investigator will make eCRFs and source documents available when requested.

In addition, the study may be evaluated by representatives of the national regulatory authorities, who will also be allowed access to study documents. The investigators should promptly notify GlaxoSmithKline Pharmaceuticals / Human Genome Sciences of any audits they have scheduled with any regulatory authority.

10.7. Drug Accountability

Upon receipt of the study agents, the designated pharmacy personnel at the study site is responsible for taking an inventory of the study agent, including any buffers or diluents. A record of this inventory must be kept and usage must be documented on study agent inventory forms provided by the sponsor.

Study agent inventory forms will be examined and reconciled by a sponsor's unblinded monitor, or designee. At the end of the study, all used and unused study agent must be accounted for on a study agent accountability form provided to the investigator by the sponsor or its designee.

10.8. Retention of Records

The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer discs or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the sponsor at the time the study is completed, terminated or discontinued.

If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the sponsor.

10.9. Financial Disclosure

The Investigator and all Sub-Investigators will provide the sponsor sufficient and accurate information on financial interests (proprietary or equity interests, payments exclusive of clinical trial costs) to allow complete disclosure to regulatory authorities. The investigators shall promptly update this information if any relevant changes occur during the course of the investigation and for a period of 1 year following study completion.

10.10. Publication Policy

This study is being conducted as part of a multi-center clinical study. Data from all sites participating in the multi-center clinical study will be pooled and analyzed. The investigator acknowledges that an independent, joint publication is anticipated to be authored by the investigators of the multi-center study and sponsor's representatives. Neither institution nor principal investigator shall independently publish or present the results of the study prior to the publication of the multi-center study publication. The investigator agrees that the sponsor will be the coordinator and arbitrator of all multi-center study publications. For multi-center trials, no investigator will be authorized to publish study results from an individual center until the earlier of the multi-center trial results are published or 12 months after the end or termination of the multi-center trial at all sites.

The investigator shall submit a copy of any proposed publication, manuscript, abstract, presentation or other document with respect to this study to the sponsor for review and comment at least 60 days prior to its submission for publication or presentation. No publication or presentation with respect to the study shall be made unless and until all of the sponsor's comments on the proposed publication or presentation have been considered and any information determined by sponsor to be confidential information has been removed. If requested in writing by the sponsor, the investigator shall withhold material from submission for publication or presentation for an additional 60 days to allow for the filing of a patent application or the taking of other measures to establish and preserve the sponsor's proprietary rights.

10.11. Study or Study Site Termination

If the sponsor, the investigator, IRB/IEC or a regulatory authority discovers conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation between the sponsor and the investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.

- A decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the product.

The study site may warrant termination under the following conditions:

- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulatory authority regulations.
- Submission of knowingly false information from the research facility to the sponsor, study monitor, or the regulatory authority.
- Insufficient adherence to protocol requirements.

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LIST OF APPENDICES

Appendix 1 American College of Rheumatology (ACR) Criteria for SLE

The ACR Criteria for the Classification of Systemic Lupus Erythematosus (Tan et al, 1982, and Hochberg, 1997)

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

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

Appendix 2 International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Classification of Lupus Nephritis

CLASS I	**MINIMAL MESANGIAL LUPUS NEPHRITIS**
	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence.
CLASS II	**MESANGIAL PROLIFERATIVE LUPUS NEPHRITIS**
	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits.
	May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy.
CLASS III	**FOCAL LUPUS NEPHRITIS**
	Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving < 50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations.
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
CLASS IV	**DIFFUSE LUPUS NEPHRITIS**
	Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥ 50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥ 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥ 50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
Class IV-G (A/C)	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
CLASS V	**MEMBRANOUS LUPUS NEPHRITIS**
	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations.
	Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed.
	Class V lupus nephritis may show advanced sclerosis.
CLASS VI	**ADVANCED SCLEROSIS LUPUS NEPHRITIS**
	≥90% of glomeruli globally sclerosed without residual activity.

Adapted from: Weening J, D'Agati V, Schwartz M, et al. The Classification of Glomerulonephritis in Systemic Lupus Erythematosus Revisited. J Am Soc Nephrol 2004; 15:241-150.

Appendix 3 SELENA SLEDAI Disease Assessment Scales

SELENA SLEDAI Score

Score if descriptor is present at time of visit or in the preceding 10 days.

Wgt.	Descriptor	Definition
8	Seizure	Recent onset (last 10 days). Exclude metabolic, infectious drug cause, or seizure due to past irreversible CNS damage.
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intellectual function with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	Visual Disturbance	Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate of hemorrhage in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes.
8	Cranial Nerve Disorder	New onset sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.
8	Lupus Headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
8	CVA	New onset of CVA(s). Exclude arteriosclerosis or hypertensive causes.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	Arthritis	More than 2 joints with pain & signs of inflammation (ie, tenderness, swelling or effusion).
4	Myositis	Proximal muscle aching/weakness associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	UrinaryCasts	Heme-granular or red blood cell casts.
4	Hematuria	> 5 red blood cells/high power field. Exclude stone, infection, or other causes.
4	Proteinuria	New onset or recent increase of more than 0.5 g/24 hours.
4	Pyuria	> 5 white blood cells/high power field. Exclude infection.
2	Rash	New or ongoing inflammatory lupus rash.
2	Alopecia	New or ongoing abnormal, patchy or diffuse loss of hair due to active lupus.
2	Mucosal Ulcers	New or ongoing oral or nasal ulcerations due to active lupus.
2	Pleurisy	Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.
2	Pericarditis	Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.
2	Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	Increased DNA Binding	> 25% binding by Farr assay or above normal range for testing laboratory.
1	Fever	> 38°C. Exclude infectious cause.
1	Thrombocytopenia	< 100,000 platelets/mm^3
1	Leukopenia	< 3,000 white blood cells/mm^3. Exclude drug causes.
	TOTAL SCORE	**(Sum of weights next to descriptors marked present)**

Adapted from:

Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI: a disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992; 35(6):630-40.

SLE Flare Index

Mild or Moderate Flare	Severe Flare
□ Change in SELENA SLEDAI instrument score of 3 points or more (but not to more than 12)	□ Change in SELENA SLEDAI instrument score to greater than 12
□ New/worse: Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus Nasopharyngeal ulcers Pleuritis Pericarditis Arthritis Fever (SLE)	□ New/worse: CNS-SLE Vasculitis Nephritis Myositis Plt < 60,000 Hemolytic anemia:Hb < 70 g/L or decrease in Hb > 30 g/L
□ Increase in prednisone, but not to > 0.5 mg/kg/day	**Requiring**: double prednisone, or prednisone increase to > 0.5 mg/kg/day, or hospitalization
□ Added NSAID or hydroxychloroquine for SLE Activity	□ Increase in prednisone to > 0.5 mg/kg/day
□ ≥1.0 increase in PGA score, but not to more than 2.5	□ New cyclophosphamide, azathioprine, methotrexate, or mycophenolate for SLE activity
	□ Hospitalization for SLE activity
	□ Increase in PGA score to > 2.5

Adapted from:

Petri M, Buyon J, Kim M. Classification and definition of major flare in SLE clinical trials. Lupus 1999; 8:685-91.

Petri M et al. Combined Oral Contraceptives in Women with Systemic Lupus Erythematosus. N Engl J Med 2005;353:2550-8.

Buyon JP et al. The Effect of Combined Estrogen and Progesterone Hormone Replacement Therapy on Disease Activity in Systemic Lupus Erythematosus: A Randomized Trial. Ann Internal Med 2005; 142 (12 Pt 1):953-62.

Physician's Global Disease Assessment

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

Appendix 4 SLICC/ACR Damage Index

Systemic Lupus International Collaborating Clinics/American College of Rheumatology
Damage Index for Systemic Lupus Erythematosus*

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

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

*Damage (nonreversible change, not related to active inflammation) occuring since onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

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

Appendix 5 Laboratory Tests

Hematology

Total white blood cell count
Differential:
- Absolute Neutrophils
  - Segmented Neutrophils
  - Band Neutrophils
  - Myelocytes
  - Metamylocytes
  - Promyelocytes
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Hemoglobin
Hematocrit
Red blood cell (RBC) count
Platelet count
Prothrombin time (PT)
Partial thromboplastin time (PTT)
Serum Pregnancy

Urinalysis

Protein
Glucose
Ketones
Occult blood
Microscopic examination including:
- WBC per hpf
- RBC per hpf
- Dysmorphic RBC
- Casts (specified by type eg, RBC, WBC)

Urine Pregnancy
Spot urine
24-hour urine
*The urine microscopy and routine urinalysis will be performed locally. All other tests will be performed by a central laboratory.

Modified Chem-20

Electrolytes:
- Sodium
- Potassium
- Magnesium
- Chloride
- Carbon dioxide
- Calcium adjusted for Albumin
- Inorganic Phosphate

Enzymes:
- SGOT (AST)
- SGPT (ALT)
- Alkaline Phosphatase
- Gamma glutamyl transferase (GGT)
- Lactic dehydrogenase (LDH)

Other:
- Creatinine
- Blood urea nitrogen (BUN)
- BUN/creatinine ratio
- Bilirubin, total
- Protein, total
- Albumin
- Uric acid
- Glucose

Biological Markers

BLyS protein
Serum complement (C3 and C4)

FACS of peripheral lymphocytes: B lymphocytes ($CD20^+$, $CD20^+/27^+$ memory, $CD20^+/27^-$ naïve, $CD20^+/69^+$ activated, $CD20^+/138^+$ plasmacytoid, $CD19^+/27^{BRIGHT}/38^{BRIGHT}$ SLE subset $CD19^+/CD24^{HIGH}/CD38^{HIGH}$ regulatory B cell and $CD20^-/138^+$ plasma cells) Note: May be collected in selected sites/regions.

Urinary Biomarkers
Include, but are not limited to, MCP-1, hepcidin, NGAL, LFABP, Angiogenin, Angiopoietin 2, Angiostatin, IL-6r, Osteopontin, PAI-1, PF4, RAGE, RANK, Sgp130, Siglec 5, Siglec 9, Tgf-beta1, TIM1, TIMP-2, TLSP, TNFR-II, Trem1, VCAM-1, Vegf-C and VEGF-R3.

Other:
Alcohol and drug screen

Infectious Disease Screening

HIV-1/2 antibody
Hepatitis C antibody
Hepatitis B surface antigen
Hepatitis B surface and core antibodies
Hepatitis B Viral DNA PCR Quantitative (HBV DNA)

Autoantibodies
ANA
Anti-dsDNA
aCL (IgG, IgA and IgM isotypes)
Anti-Sm
Anti-c1q

Immunoglobulins

Serum immunoglobulin isotypes: IgG, IgM, IgA

Belimumab PK and Immunogenicity

Appendix 6 Pharmacogenetic Research

Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in different populations. There is increasing evidence that an individual's genetic composition (ie, genotype) may impact pharmacokinetics, pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability).

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Research Rationale

Blood samples for pharmacogenetics will be drawn as described in Section 9. Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analyses to be conducted if there is unexplained or unexpected variation in response to belimumab.

If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with belimumab that may be attributable to genetic variations of subjects, the following objectives may be investigated:

- Relationship between genetic variants and the pharmacokinetics of belimumab.
- Relationship between genetic variants and safety and/or tolerability of belimumab.
- Relationship between genetic variants and efficacy of belimumab.

Study Population

Any subject who has given informed consent to participate in the clinical study, has met all the entry criteria for the clinical study, and receives belimumab may take part in the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

Study Assessments and Procedures

In addition to any blood samples drawn for the clinical study, a whole blood sample (~10 mL) will be collected for the PGx research at baseline. The PGx sample is labeled (or coded) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample. The blood samples should be drawn on Day 0 (baseline), provided informed consent for PGx research has been obtained from the subject, but the sample may be taken at any time while the subject is participating in the clinical study.

If deoxyribonucleic acid (DNA) is extracted from the blood sample, the DNA will be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or set of studies) of belimumab has been completed and the study data reviewed. In some cases, the samples may not be studied.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or the sponsor may destroy the samples sooner. The sponsor or those working with the sponsor (for example, other researchers or a contract lab) will use samples collected from the study for the purpose stated in this protocol and in the subject informed consent form.

Subjects may request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research and has a sample taken for PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options:

1. The sample is retained for PGx research.
2. The sample is destroyed.

If a subject withdraws consent from the PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by the sponsor and maintain the documentation in the site study records. In either case, the sponsor will only use study information collected/generated up to that point.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by the sponsor and maintain the documentation in the site study records.

Pharmacogenetic Analyses

Specific sections of DNA may be selected from areas of the genome (ie, candidate genes). The candidate genes could include the drug target, the drug target pathway, drug metabolizing enzymes, genes associated with mechanisms underlying adverse events, and genes associated with the study disease.

In addition, a genome-wide scan or large scale sequencing of polymorphic markers located across the genome may be implemented. This approach is often employed when potential genetic effects are not well understood.

Other new technologies may be developed to help us better study and understand genetic variants associated with drug response.

Continuing research may identify other enzymes, transporters, proteins, or receptors that may be involved in response to belimumab. The genes that may code for these proteins may also be studied.

Components of the PGx analysis may include:

- Hardy-Weinberg Equilibrium testing

  The genotypic frequencies of each polymorphism will be evaluated for conformity to those expected under normal conditions by employing Hardy-Weinberg Equilibrium testing.

- Comparison of Demographic and Baseline Characteristics by Genotype

  Differences in baseline clinical characteristics and potential contributing covariates may be summarized and compared among genotype (or haplotype) subgroups.

- Evaluation of Genotypic Effects

  Analyses may be carried out to evaluate the degree of association between subject's genotype (or haplotype) and selected parameters (eg, pharmacokinetics, disease activity and safety). Where such genotypic tests are inappropriate (eg, where the number of marker genotypes is too large and/or the frequency of individual genotypes too small), allelic tests may be conducted. Allelic tests evaluate whether the frequency of each marker allele is the same in responders and non-responders.

- Evaluation of Treatment by Genotype and Gene-Gene Interaction

  In addition to evaluating the main effects of the genotypes (haplotypes or alleles) on the selected parameters, the possibility of a treatment group by genotype (haplotype or allele) interaction will also be explored. If appropriate, the joint effects of multiple markers (gene-gene interactions) may also be evaluated.

- Linkage Disequilibrium

  For pairs of polymorphisms, the degree to which alleles from the 2 sites are correlated (linkage disequilibrium) may also be evaluated. If the genotypes at 2 polymorphic sites within a gene are shown to be statistically associated with a response to study agent, the degree of linkage disequilibrium will aid interpretation in that it will indicate the extent to which the 2 sites are exerting independent effects.

- Multiple Comparisons and Multiplicity

  Adjustment to observed p-values may be made to limit erroneous conclusions due to multiple tests when multiple markers are evaluated (especially in the case of a genome scan for association).

- Power and Sample Size Considerations

  The ability to detect differential drug response among genotypes at a polymorphic site depends on the total number of subjects genotyped and the frequency distribution of the different genotypes. Consequently, genotyping analyses are plausible for those polymorphic sites where the number of subjects comprising the genotypic groups is sufficiently large; however, these frequencies will not be known until sufficient samples have been collected and genotyping is complete. These examples show that small sample sizes typically encountered in Phase 1 and Phase 2 studies may be sufficient to identify clinically relevant genetic associations.

Additional analyses may be conducted as necessary.

Provision of Study Results and Confidentiality of Subject's PGx Data

The sponsor may summarize the cumulative PGx research results in the clinical study report or in a separate report. In general, the sponsor does not inform the investigator, subject or anyone else (eg, family members, study investigators, primary care physicians, insurers, or employers) of the PGx research results because the information generated from PGx studies is preliminary in nature, and the significance and scientific validity of the results are undetermined at such an early stage of research, under any circumstance unless required by law.

Appendix 7 Adverse Event Severity Grading Tables

SKIN (INJECTION SITE)	GRADE 1 MILD	GRADE 2 MODERATE[1]	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Induration	< 15mm	15-30 mm	> 30mm	n/a
Erythema	< 15mm	15-30 mm	> 30mm	n/a
Edema	< 15mm	15-30 mm	> 30mm	n/a
Rash at Injection Site	< 15mm	15-30 mm	> 30mm	n/a
Pruritus	slight itching at injection site	moderate itching at injection extremity [1]May be assessed as mild despite the size if event is transient (< 48 hours) with mild discomfort; no medical intervention/therapy required	itching over entire body	n/a

Modified from DMID Adult Toxicity Tables, 2007

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

(continued)

*ULN = Upper Limit of Normal.

Modified from DMID Adult Toxicity Tables, 2001

CARDIOVASCULAR	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cardiac Arrhythmia	-	Asymptomatic/transient; dysrhythmia; no treatment req	Recurrent/persistent dysrhythmia. Symptomatic; treatment req	Unstable dysrhythmia hospitalization and treatment required
Hypotension	Transient orthostatic hypotension, no treatment	Symptoms correctable with oral fluid treatment	IV fluid req, no hospitalization req	Hospitalization req
Hypertension	Transient, increase > 20 mm/Hg; no treatment	Recurrent; chronic increase > 20 mm/Hg, treatment req	Acute treatment req; out patient hospitalization possible	Hospitalization req
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion, pain, ECG changes	Tamponade OR pericardiocentesis OR surgery req
Hemorrhage, Blood Loss	-	Mildly symptomatic; no treatment required	Gross blood loss OR 1-2 units transfused	Massive blood loss OR > 2 units transfused

(continued)

Modified from DMID Adult Toxicity Tables, 2001

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

(continued)

Modified from DMID Adult Toxicity Tables, 2001

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

(continued)

*(Goldfarb et al, 2001; Yamani et al, 2001; Eibl and Rosen, 1995).

Modified from DMID Adult Toxicity Tables, 2001

GASTROINTESTINAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Nausea	Mild OR transient; reasonable intake maintained	Mod discomfort OR intake decreased for < 3 days	Severe discomfort OR minimal intake for ≥ 3 days	Hospitalization required
Vomiting	Mild OR transient; 2-3 episodes/day OR mild vomiting lasting < 1 week	Mod OR persistent; 4-5 episodes per day; OR vomiting lasting ≥ 1 week	Severe vomiting of all foods/fluids in 24 hours OR orthostatic hypotension OR IV treatment req	Hypotensive shock OR hospitalization required for IV treatment req
Diarrhea	Mild or transient; 3-4 loose stools per day OR mild diarrhea lasting < 1 week	Mod OR persistent; 5-7 loose stools per day or diarrhea lasting ≥ 1 week	Bloody diarrhea; OR orthostatic hypotension OR > 7 loose stools/day OR IV treatment req	Hypotensive shock OR hospitalization req
Oral Discomfort/Dysphagia	Mild discomfort, no difficulty swallowing	Difficulty swallowing but able to eat and drink	Unable to swallow solids	Unable to drink fluids; IV fluids req
Constipation	Mild	Moderate	Severe	Distention with vomiting

(continued)

Modified from DMID Adult Toxicity Tables, 2001

RESPIRATORY	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cough (for aerosol studies)	Transient; no treatment	Treatment associated cough; inhaled bronchodilator	Uncontrolled cough; systemic treatment req	-
Bronchospasm Acute	Transient; no treatment; FEV1 70% to < 80% (or peak flow)	treatment req; normalizes with bronchodilator; FEV1 50% to < 70% (or peak flow)	No Normalization with bronchodilator; FEV 25% to < 50% (or peak flow), retractions	Cyanosis; FEV1 < 25% (or peak flow) OR intubated
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring O2 therapy

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

(continued)

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

Modified from DMID Adult Toxicity Tables, 2001

MISCELLANEOUS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fever (oral > 12 hours)	37.7-38.5°C or 100.0-101.5°F	38.6-39.5°C OR 101.6-102.9°F	39.6-40.5°C OR 103-105°F	> 40.5°C OR > 105°F
Headache	Mild; No treatment req	Mod; or non-narcotic analgesia treatment	Severe; OR responds to initial narcotic treatment	Intractable; OR requiring repeated narcotic treatment
Allergic Reaction	Pruritus without rash	Localized urticaria	Generalized urticaria angioedema	Anaphylaxis
Cutaneous/Rash/ Dermatitis	Erythema, pruritus rash OR dry desquamation	Diffuse maculopapular OR dry desquamation	Vesiculation OR moist desquamation ulceration	ANY ONE: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, necrosis req surgery, exfoliative dermatitis
Local Reaction (secondary to parenteral treatment- not vaccination or skin test)	Erythema	Induration < 10 mm OR inflammation OR phlebitis	Induration > 10 mm OR ulceration	Necrosis of skin
Fatigue	Normal activity Reduced < 25%	Normal activity Reduced 25-50%	Normal activity reduced > 50%; cannot work	Unable to care for self

(continued)

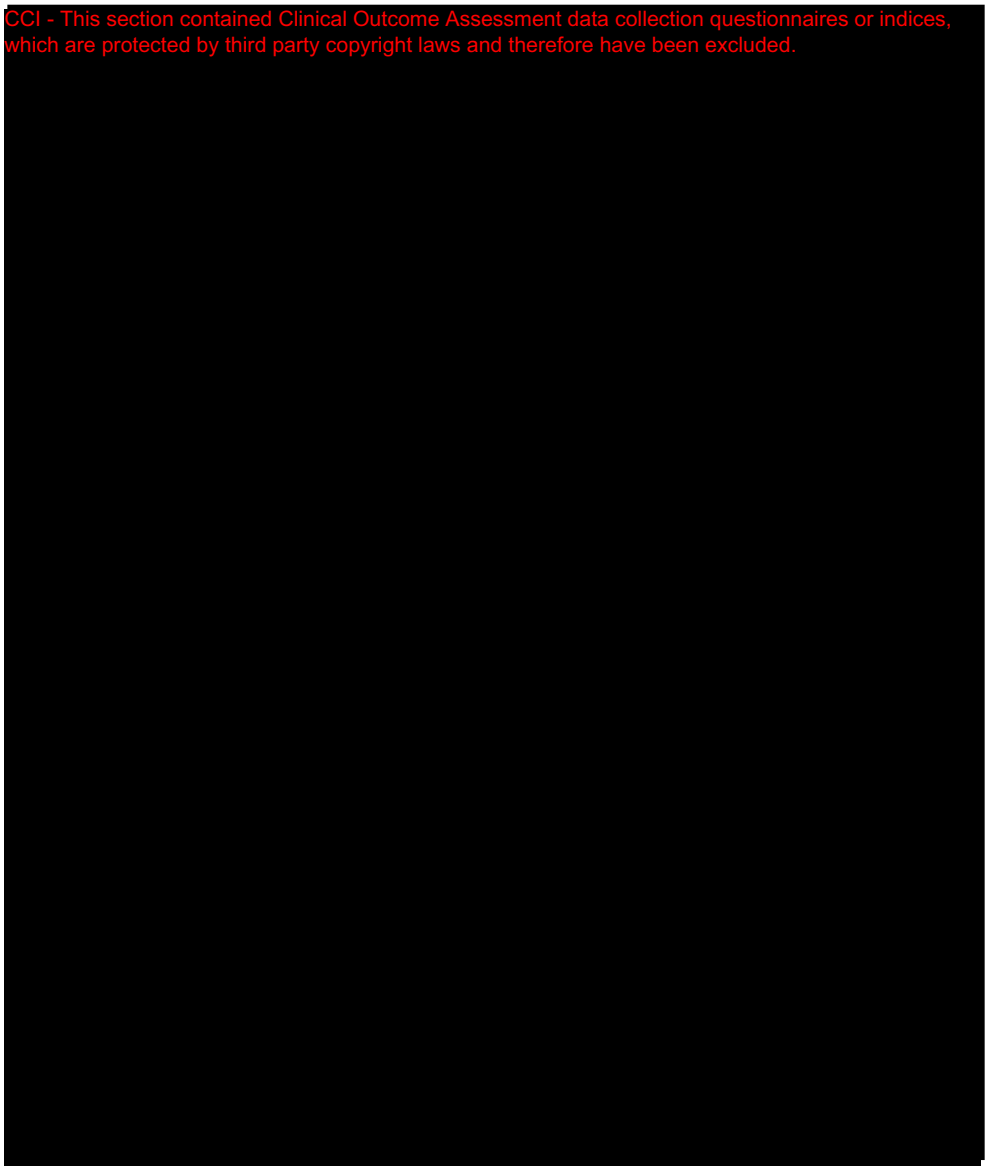
Modified from DMID Adult Toxicity Tables, 2001

NEUROLOGIC	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuro-cerebellar	Slight incoordination OR dysdiadochokinesia	Intention tremor OR dysmetria OR slurred speech OR nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with ADLs	Unable to stand
Neuro-psych/ mood	-	none	Severe mood changes requires medical intervention	Acute psychosis requiring hospitalization
Paresthesia (burning, tingling, etc)	Mild discomfort; no treatment needed	Mod discomfort non-narcotic analgesia req	Severe discomfort; OR narcotic analgesia req with symptomatic improvement	Incapacitating; OR not responsive to narcotic analgesia
Neuro-motor	Mild weakness in muscle of feet but able to walk and/or mild increase or decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes), mild weakness in hands, still able to do most hand tasks and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop), and mod proximal weakness ie, in hands interfering with ADLs and/or requiring assistance to walk and/or unable to rise from chair unassisted	Confined to bed or wheelchair because of muscle weakness
Neuro-sensory	Mild impairment sensations, (ie, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment mod de-sensation, (ie, of vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical.	Severe impairment (dec or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (ie, upper and lower extremities)	Sensory loss involves limbs and trunk

(concluded)

Modified from DMID Adult Toxicity Tables, 2001

Appendix 8 Columbia- Suicide Severity Rating Scale (C-SSRS) Baseline/Screening

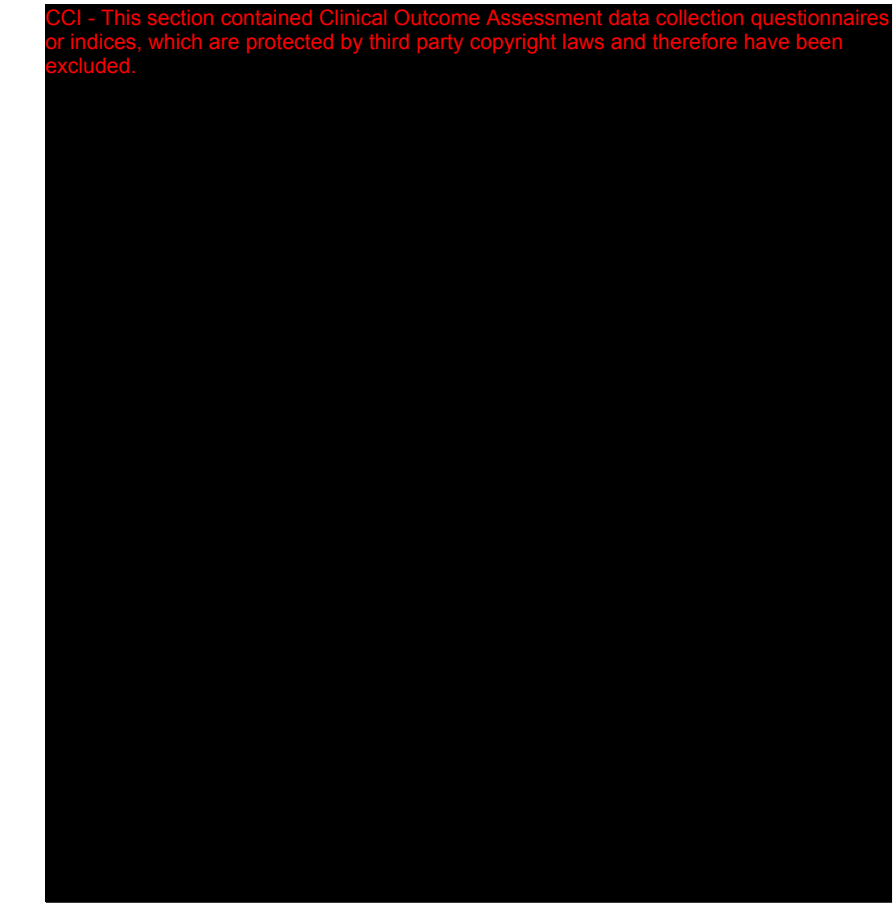


CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Appendix 9 Columbia- Suicide Severity Rating Scale (C-SSRS) Since Last Visit

Columbia Suicide-Severity Rating Scale (C-SSRS) Since Last Visit

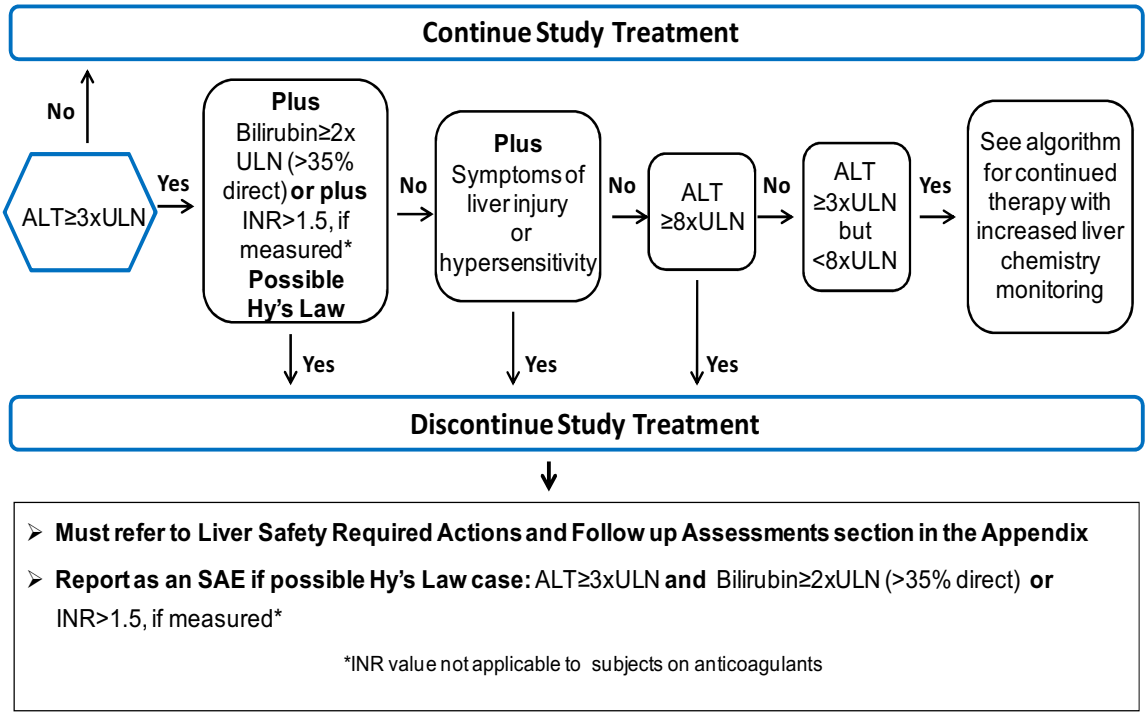
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



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.

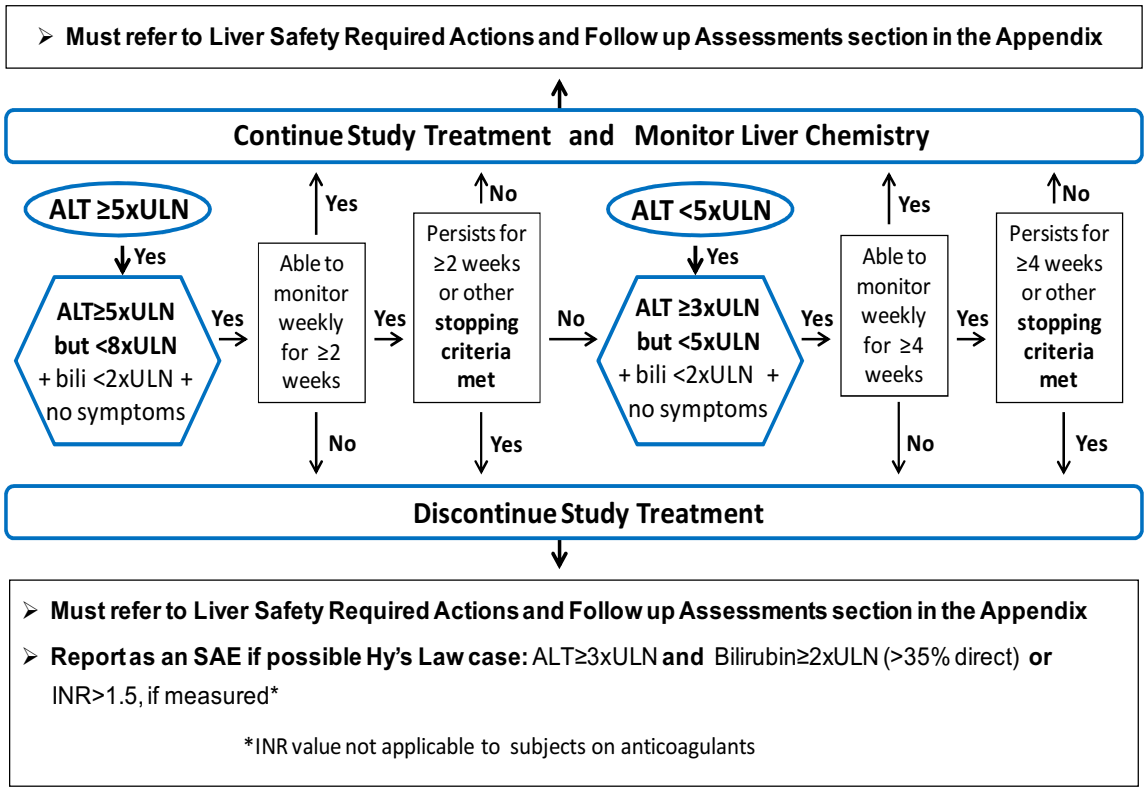
Appendix 10 Algorithm for Liver Chemistry Stopping and Follow-up Criteria

Liver Stopping Event Algorithm



- Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.7.2.1 and Section 6.7.3.1.

Liver Monitoring Event Algorithm with Continued Therapy for ALT≥3xULN but <8xULN



- Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.7.2.1 and Section 6.7.3.1

References

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

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Appendix 11 Possible Suicidality Related History Questionnaire (PSRHQ)

CONFIDENTIAL

Protocol Identifier	BEL114054

Final - 15 JAN 13

POSSIBLE SUICIDALITY-RELATED HISTORY QUESTIONNAIRE (PSRHQ) INSTRUCTIONS

The Possible Suicidality Related History Questionnaire (PSRHQ) eCRF is to be completed only once during the entire study when the following conditions have been met the first time:

- If a "Yes" response is given on the Columbia Suicide-Severity Rating Scale (C-SSRS) to suicidal ideation questions 3, 4, or 5.

And/or

- If a "Yes" response is given on the Columbia Suicide-Severity Rating Scale (C-SSRS) to any suicidal behavior questions.

Check either the "Yes" or "No" box to indicate whether the subject has any SLE-related neuropsychiatric event(s) prior to starting the study.

If "Yes", select neuropsychiatric event(s) that apply and enter the most recent date of occurrence.

US:ENG (United States/English) Non-standard[PSRHQ]

GlaxoSmithKline CONFIDENTIAL Final - 15 JAN 13

Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
BEL114054			

Date of assessment ☐☐ Day ☐☐☐ Month ☐☐ Year

POSSIBLE SUICIDALITY-RELATED HISTORY QUESTIONNAIRE

Has the subject had any SLE-related neuropsychiatric events prior to study start?

[Y] ☐ Yes [N] ☐ No

If Yes, check all that apply and provide the most recent date of occurrence:

	Event	Date (DDMMMYYYY)
☐	Acute Confusional State	
☐	Acute Inflammatory Demyelinating Polyradiculoneuropathy (Guillain-Barre Syndrome)	
☐	Anxiety Disorder	
☐	Aseptic Meningitis	
☐	Autonomic Disorder	
☐	Cerebrovascular Disease	
☐	Cognitive Dysfunction	
☐	Demyelinating Syndrome	
☐	Headache	
☐	Mononeuropathy Single	
☐	Mononeuropathy Multiplex	
☐	Mood Disorders	
☐	Movement Disorder (Chorea)	
☐	Myasthenia Gravis	
☐	Myelopathy	
☐	Neuropathy, Cranial	
☐	Plexopathy	
☐	Polyneuropathy	
☐	Psychosis	
☐	Seizures and Seizure Disorders	

Appendix 12 Possible Suicidality Related Questionnaire (PSRQ)

CONFIDENTIAL

Protocol Identifier	BEL114054

Final - 15 JAN 13

POSSIBLE SUICIDALITY-RELATED QUESTIONNAIRE (PSRQ) INSTRUCTIONS

The Possible Suicidality Related Questionnaire (PSRQ) is to be completed every time the following conditions have been met:

- If a "Yes" response is given on the Columbia Suicide-Severity Rating Scale (C-SSRS) to suicidal ideation questions 3, 4, or 5

And/or

- If a "Yes" response is given on the Columbia Suicide-Severity Rating Scale (C-SSRS) to any suicidal behavior questions

Check either the "Yes" or "No" box to indicate whether the subject is currently using illicit drugs. If "Yes", select all illicit drugs that apply. If "Other" is selected, provide an explanation in the space provided.

Ensure the selected illicit drugs are entered on the Concomitant Medications eCRF.

Check either the "Yes" or "No" box to indicate whether the subject is currently using alcohol. If "Yes", specify the average units per week.

- 1 unit of alcohol = 1 measure of spirits, ½ pint of beer, 1 small glass of wine

Check either the "Yes" or "No" box to indicate whether the subject has experienced any recent stress. If "Yes", select all factors that apply. If "Other" is selected, provide an explanation in the space provided.

Check either the "Yes" or "No" box to indicate whether the subject has any family history of suicidality. If "Yes", select all ideation(s) and/or behavior(s) that apply.

Check either the "Yes" or "No" box to indicate whether the subject has a family history of psychiatric disorders. If "Yes", provide an explanation in the space provided next to all that apply

US:ENG (United States/English) Non-standard[PSRQ]

GlaxoSmithKline CONFIDENTIAL Final - 15 JAN 13

Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
BEL114054			

Date of assessment ☐☐ Day ☐☐☐ Month ☐☐ Year

POSSIBLE SUICIDALITY-RELATED QUESTIONNAIRE (PSRQ)

☐ Not Done

Is the subject currently using illicit drugs? [Y] ☐ Yes [N] ☐ No

If Yes, check all that apply:

☐ Amphetamines ☐ Benzodiazepines ☐ Cannabinoids ☐ Cocaine ☐ Opiates

☐ Other, Specify: _____

Is the subject currently using alcohol? [Y] ☐ Yes [N] ☐ No

If Yes, Average Unit(s) of Alcohol/Week: _____

Has the subject experienced any recent stress? [Y] ☐ Yes [N] ☐ No

If Yes, check all that apply:

☐ Family Problems ☐ Relationships ☐ Employment/ Unemployment ☐ Finances

☐ Other Factors, Specify: _____

Any family history of suicidality? [Y] ☐ Yes [N] ☐ No

If Yes, check ideation and/or behavior next to all that apply:

Father	☐ Ideation	☐ Behavior
Mother	☐ Ideation	☐ Behavior
Sibling	☐ Ideation	☐ Behavior
Other	☐ Ideation	☐ Behavior

Any family history of psychiatric disorders? [Y] ☐ Yes [N] ☐ No

If Yes, specify disorder next to all that apply:

Father _____

Mother _____

Sibling _____

Other _____

US:ENG (United States/English) Non-standard[PSRQ]

Appendix 13 Country-specific Requirements: Thailand

Protocol Amendment 02-Thailand, 16 August 2012

Summary of Modifications and Rationale:

The recommended duration of study agent infusion was changed from 1 hour to approximately 2-3 hours. This change was made to accommodate clinical practice in Thailand in which the normal IV infusion rate is generally between 80-150 mL/h; the volume of study agent to be infused IV (250 mL) was not changed.

Detailed Description of Changes

Section 5.3 Dose, Route of Administration, and Schedule

Formerly:

The treatment groups include one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving standard of care therapy (as described in Section 5.5.1). All study agent treatments will be administered intravenously ~~over 1 hour~~. Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days days thereafter through 100 weeks of double-blind treatment. Following the final double-blind visit at Week 104, subjects who complete 100 weeks of treatment with study agent and complete Week 104 assessments, will have the option to continue in the 6-month open-label extension period (with first dose given at the Week 104 visit).

Modified to:

The treatment groups include one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving standard of care therapy (as described in Section 5.5.1). All study agent treatments will be administered intravenously over **approximately 2 – 3 hours**. Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days days thereafter through 100 weeks of double-blind treatment. Following the final double-blind visit at Week 104, subjects who complete 100 weeks of treatment with study agent and complete Week 104 assessments, will have the option to continue in the 6-month open-label extension period (with first dose given at the Week 104 visit).

CLINICAL PROTOCOL HGS1006-C1121
Protocol Amendment: 00
EudraCT Number: 2011-004570-28
Date: 19 October 2011

TITLE OF STUDY:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Belimumab plus Standard of Care versus Placebo plus Standard of Care in Adult Subjects with Active Lupus Nephritis

STUDY SPONSOR: Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, Maryland 20850
U.S.A.

Confidential and Proprietary

Investigator Agreement

I will provide copies of the protocol, any subsequent amendments and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational study agent and the study protocol. I agree to conduct this clinical trial according to the protocol described herein, except when mutually agreed to in writing with the sponsor. I also agree to conduct this study in compliance with Good Clinical Practice (GCP) standards as defined by the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice, all applicable national, state, and local regulations, as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) and any other institutional requirements.

Principal Investigator:

Signature *Date (dd mmm yy)*

Name (please type or print)

Institution

Address

Study Synopsis

Study Number: HGS1006-C1121

Title of the Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Belimumab plus Standard of Care versus Placebo plus Standard of Care in Adult Subjects with Active Lupus Nephritis

Clinical Development Phase: 3

Objectives:

- To evaluate the efficacy of belimumab in combination with standard of care in adult subjects with lupus nephritis Class III, IV or V using the 2003 ISN/RPS criteria.
- To assess the safety and tolerability of belimumab plus standard of care versus placebo plus standard of care in adult subjects with lupus nephritis Class III, IV or V using the 2003 ISN/RPS criteria.

Diagnosis & Inclusion Criteria: Subjects enrolled in the study must meet the following inclusion criteria:

1. Males or females at least 18 years of age.
2. Have a clinical diagnosis of SLE according to the American College of Rheumatology (ACR) criteria (Appendix 1).
3. Have active, biopsy-proven proliferative lupus nephritis Class III or IV (excluding Class III(C), IV-S(C) and IV-G(C)) either with or without the presence of Class V, or pure Class V membranous using the 2003 ISN/RPS criteria (Appendix 2); the biopsy must be performed in the 6 months prior to baseline (Day 0). Whenever possible, a tissue sample from the renal biopsy used to qualify the subject will be collected and sent to a central reading center; however, the tissue sample will not be shipped prior to nor be used for the purposes of randomization.
4. Have unequivocally positive ANA test results defined as an ANA titer ≥ 1:80 (based on Hep-2 immunofluorescence assay) and/or a positive anti-dsDNA (≥ 30 IU/mL based on ELISA assay) serum antibody test at the screening visit based on the study's central laboratory results.
5. Have documentation of active renal disease at screening requiring initiation of induction therapy with high dose corticosteroids (HDCS) with either IV cyclophosphamide (CYC) or mycophenolate mofetil (MMF) or other oral forms of mycophenolate. Induction therapy should be started no more than 14 days prior to the baseline visit (Day 0). The following factors will be used to define active renal disease:
    - Urinary protein:creatinine ratio of ≥ 1.0 AND active urinary sediment as defined by at least 1 of the following (in absence of menses and genitourinary tract infection).

- > 5 red blood cell (RBC)/high power field (hpf) or above the laboratory reference range.
- > 5 white blood cell (WBC)/hpf (or above the laboratory reference range).
- Presence of cellular casts (RBC or WBC).

- Subjects without active urinary sediment are eligible if they meet at least 1 of the following criteria:
  - Have a confirmatory biopsy performed within 3 months prior to the baseline visit meeting the criteria outlined in criterion 3
  - Have proteinuria ≥ 3.5 grams/day.

6. A female subject is eligible to enter the study if she is:
   - Not pregnant or nursing;
   - Of non-childbearing potential (ie, women who had a hysterectomy, are postmenopausal which is defined as 1 year without menses, have both ovaries surgically removed or have current documented tubal ligation or any other permanent female sterilization procedure); or
   - Of childbearing potential (ie, women with functional ovaries and no documented impairment of oviductal or uterine function that would cause sterility). This category includes women with oligomenorrhoea [even severe], women who are perimenopausal or have just begun to menstruate. These women must have a negative serum pregnancy test at screening, and agree to 1 of the following:
     - Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent; or
     - Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during study and 16 weeks after the last dose of study agent:
       - Implants of levonorgestrel or etonogestrel;
       - Ethinyl estradiol/Etonogestrel vaginal ring;
       - Injectable progesterone;
       - Any intrauterine device (IUD) with a documented failure rate of less than 1% per year;
       - Oral contraceptives (either combined or progesterone only);
       - Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) with spermidical foam/gel/film/cream/suppository;
       - Transdermal contraceptive patch;
       - Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for the female subject.
7. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information) and comply with the study protocol procedures (including required study visits).

Exclusion Criteria: Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Subjects who have previously failed induction therapy with both CYC and MMF (or other forms of mycophenolate) based on the investigator's opinion. If a subject has failed only 1 of the 2 therapies for induction, they may be eligible for study inclusion if they are newly initiating the other induction therapy (ie, a subject who failed MMF is eligible if newly initiating induction therapy with CYC or a subject who failed CYC is eligible if newly initiating induction therapy with MMF).
2. Subjects who have previously received an induction therapy within 6 months prior to the screening visit.
3. Subjects who receive CYC whose pre-induction leukocyte count is Grade 3 or 4 based on the Adverse Event Severity Grading Tables (Appendix 7).
4. Known hypersensitivity or contraindication to any drug products or any component of these drug products they plan to receive (eg, CYC, MMF, azathioprine (AZA), corticosteroids).
5. Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.
6. Have received treatment with belimumab at anytime.
7. Received any of the following within 364 days of baseline (Day 0):
   - Nitrogen mustard
   - Chlorambucil
   - Vincristine
   - Procarbazine
   - Etoposide
   - Abatacept
   - Treatment with any B cell targeted therapy (eg, rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI-Fc, or LY2127399 [anti-BAFF])
   - A biologic investigational agent (eg, abetimus sodium, anti-CD40L antibody [BG9588/ IDEC-131]). Investigational agent applies to any drug not approved for sale in the country in which it is being used.
8. Received any of the following within 90 days of baseline (Day 0):
   - Anti-TNF therapy (eg, adalimumab, etanercept, infliximab)
   - Interleukin-1 receptor antagonist (anakinra).
   - Intravenous immunoglobulin (IVIG).
   - Plasmapheresis.
9. Received a non-biological investigational agent within 60 days of baseline (Day 0).
10. Received a live vaccine within 30 days of baseline (Day 0).
11. 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 baseline (Day 0).
12. Have a history of a major organ transplant (eg, heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant or are due to receive transplantation.
13. Subjects who have been on dialysis within 364 days of baseline (Day 0).

14. An estimated glomerular filtration rate < 30 ml/min at the screening visit (using the simplified Modification of Diet in Renal Disease [MDRD] equation).
15. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to SLE (ie, cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, 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 a planned surgical procedure or a history of any other medical disease (eg, cardiopulmonary), laboratory abnormality, or condition (eg, poor venous access) that, in the opinion of the principal investigator, makes the subject unsuitable for the study.
17. Have a history of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix.
18. Have required management of acute or chronic infections, as follows:
    - Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
    - Hospitalization for treatment of infection within 60 days of baseline (Day 0).
    - Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of baseline (Day 0).
19. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to baseline (Day 0).
20. Have a historically positive test or test positive at screening for HIV antibody, hepatitis B surface antigen, or hepatitis C antibody.
21. Have an IgA deficiency (IgA level < 10 mg/dL).
22. Have a Grade 3 or greater laboratory abnormality based on the Adverse Event Severity Grading Tables (Appendix 7) except for the following that are allowed:
    - Urinalysis (eg, proteinuria)
    - Hematuria
    - Pyuria
    - Casts
    - Hypoalbuminemia due to lupus nephritis
    - Stable Grade 3 prothrombin time (PT) secondary to warfarin treatment.
    - Stable Grade 3 partial thromboplastin time (PTT) due to lupus anticoagulant and not related to liver disease or anti-coagulant therapy.
    - Stable Grade 3 gamma glutamyl transferase (GGT) elevation due to lupus hepatitis, and not related to alcoholic liver disease, uncontrolled diabetes or viral hepatitis. If present, any abnormalities in the ALT and/or AST must be ≤ Grade 2.
    - Stable Grade 3 neutropenia or stable Grade 3 white blood cell count. (Note that WBC count should be obtained immediately prior to starting induction therapy. If immediate pre-induction WBC is not available, a WBC count obtained within 28 days prior to induction may be used).
23. Subjects who 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 Columbia-Suicide Severity Rating Scale (C-SSRS) (Appendix 8) in the last 2 months or who in the investigator's opinion, pose a significant suicide risk.

Study Design and Schedule:

This is a Phase 3, multi-centre, multi-national, randomized, double-blind, placebo controlled study to evaluate the efficacy and safety of intravenous belimumab 10 mg/kg plus standard of care compared to placebo plus standard of care in adult subjects with active lupus nephritis. Subjects who meet the eligibility criteria during screening will be randomized to 1 of 2 treatment groups in a 1:1 ratio: 10 mg/kg belimumab plus standard of care or placebo plus standard of care. The randomization of all eligible subjects will be stratified by their induction regimen (high dose cortiocsteroids [HDCS] plus CYC vs HDCS plus MMF) and race (black race vs other). Subjects will be dosed with study agent on Days 0 (baseline), 14, 28 and then every 28 days through 100 weeks with a final evaluation for the double-blind treatment period at 104 weeks. Approximately 464 lupus nephritis subjects will be randomized with a target of 232 subjects in the belimumab treatment group and 232 in the placebo group. All subjects will receive background therapy consisting of one of the following standard of care regimens:

- High Dose Corticosteroids (HDCS) + Cyclophosphamide (CYC) for induction therapy followed by Azathioprine (AZA) for maintenance therapy

  OR

- HDCS + Mycophenolate Mofetil (MMF) for induction followed by MMF for maintenance therapy

The standard of care medications are described in Section 5.5.1.

All subjects will start the above induction therapy within 14 days prior to the baseline (Day 0) visit. This will allow subjects to be screened and potentially enrolled so they will not be excluded on the basis of necessary acute management. If an induction regimen has been received within 6 months prior to the screening visit, the subject will be excluded. The primary efficacy endpoint of a renal response (defined below) will be determined by changes in urinary sediment, proteinuria, and renal function at Week 104. For the renal function assessments at baseline, Week 24, 48, 52, 76, 100 and 104, the glomerular filtration rate (GFR) will be based on creatinine clearance determined from the mean creatinine value of 2 contiguous 24 hour urine collections and 2 serum creatinine measurements (first serum creatinine collected at initial visit and the second sample taken 3 days later at the follow-up visit). Subjects will be provided with the materials for collecting the two 24 hour urine collections beginning the next morning following their initial clinic visit. On the third day following the initial visit, subjects will return to the clinic for the second serum creatinine sample. For all other study visits, GFR will be estimated using the simplified MDRD formula and the urinary protein: urinary creatinine will be used for proteinuria.

For the urinary sediment assessments, both menstrual cycles and genitourinary tract infections may be confounders. The urine collection may be postponed up to 14 days at the investigators discretion if menstrual bleeding or a genitourinary tract infection is present at anytime during the 24 hour urine collection.

Renal response will be measured as complete, partial, or no response based on study defined criteria (see Section 8.5). Week 104 renal response will be defined by a response at Week 100 that is confirmed by a repeat measurement at Week 104.

All subjects who discontinue treatment during the double-blind period (for reasons other than receipt of prohibited medications or doses of medications that result in treatment-failure designation or withdrawal of consent) should return for the scheduled visits through Week 104. For subjects who discontinue study treatment due to receipt of prohibited medications, an Exit visit should be completed approximately 4 weeks after the last dose of study agent and a Follow-up visit approximately 8 weeks after the last dose of study agent.

In the event that a subject withdraws consent from the study, an attempt should be made to obtain consent for mortality status at Week 104. Any subject that withdraws consent for use and disclosure of research-related health information will be considered withdrawn from the study and not followed for mortality.

Subjects who successfully complete the initial 104-week double blind period may enter into a 6-month open-label extension. The Week 104 visit of the double-blind period will serve as the Day 0 visit for subjects entering the open-label extension. In the open-label extension, all subjects will receive 10 mg/kg belimumab every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the last dose). The first dose on the open-label extension will be given at the Week 104 visit of the double-blind period following the completion of all Week 104 assessments. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety as per the study calendar (see Table 6-3). Subjects who complete the 104-week double-blind period, but do not enter the open label extension will be required to return for an additional follow up visit 8 weeks after the last dose of study agent. All subjects who enter the open-label extension period and withdraw early will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent.

At the end of the 6-month open-label extension period, subjects who wish to continue treatment may do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may continue to receive belimumab under this protocol until belimumab becomes commercially available.

Efficacy Endpoints and Analysis:

The primary efficacy endpoint is renal response at Week 104 measured as an ordinal response - complete renal response, partial renal response, or no renal response. Renal response is determined by changes in urinary sediment, proteinuria, and renal function. Renal response at Week 104 will be defined by a response at Week 100 that is confirmed by a repeat measurement at Week 104. Renal response is defined as follows:

- Complete Renal Response

  Calculated glomerular filtration rate (GFR) is within normal range

  AND

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

  AND

  Urinary protein:creatinine ratio < 0.5

  (Note: For subjects with a normal urinary sediment and GFR at baseline and only the presence of proteinuria (≥ 3.5 grams/day), the urine protein:creatinine ratio should be < 0.5 to meet the primary endpoint)

- Partial Renal Response

  Estimated or calculated GFR no more than 10% below the baseline value or within normal range

  AND

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

  AND

  ≥ 50% decrease in the urine protein:creatinine ratio with one of the following:
  - a urine protein:creatinine ratio of < 1.0, if the baseline ratio was ≤ 3.0
    OR
  - a urine protein:creatinine ratio of < 3.0, if the baseline ratio was > 3.0

- No Renal Response

  Not meeting criteria for either complete or partial renal response

Major Secondary Endpoints:

- Renal response (complete, partial or no response) at Week 52.
- Proportion of subjects who achieve complete renal response at Week 104.

Sample Size Calculation:

It is expected that approximately 50% subjects on placebo plus standard of care will have complete (10%) or partial renal response (40%) at the Week 104 visit (Appel et al, 2009; Sinclair, 2007). It is expected that renal response in subjects on belimumab plus standard of care will be approximately 65% (Complete = 15%, Partial = 50%). Approximately 464 subjects will be randomized to achieve a target of 232 subjects in each treatment arm providing approximately 90% power to detect the difference in the primary endpoint, based on a 2-sided Van Elteren test at the 5% significance level (Zhao et al, 2008).

Analysis of Primary Efficacy Endpoint:

Renal response (complete, partial, or no renal response) at the Week 104 visit will be compared between the belimumab plus standard of care treatment group and placebo plus standard of care using the Van Elteren test, stratified by the baseline randomization factors. Any subject who receives a protocol-prohibited medication or protocol prohibited dose (as defined in Sections 5.5 and 5.6) will be considered a treatment failure (ie, non-responder) for the primary endpoint.

Analysis of Major Secondary Efficacy Endpoints:

Renal response (complete, partial or no response) at the Week 52 visit will be analyzed using the same method as for the primary endpoint. The proportion of subjects who achieve a complete renal response at the Week 104 visit, will be compared between the belimumab treatment group and placebo group using a logistic regression model. The independent variables in the model will include treatment group (ie, 10 mg/kg belimumab vs placebo) and the baseline randomization stratification factors.

For the analysis of the primary and the major secondary efficacy endpoints, a step-down sequential testing procedure will be used to control the overall type 1 error (Section 8.1).

Other efficacy endpoints are described in Section 8.5.4.

Safety Endpoints and Analysis:

Descriptive statistics will be used to summarize adverse events (AEs), changes in laboratory parameters and immunogenicity. The frequency and rate of laboratory abnormalities will be tabulated by treatment group. The frequency and rate of adverse events will be tabulated by MedDRA system organ class (SOC) and preferred term and compared between placebo and the belimumab treatment group.

An independent Data Monitoring Committee (DMC) will review unblinded safety data on an ongoing basis until data through Week 104 of the double-blind treatment period are locked and analyzed (after which time monitoring may be assumed by an internal HGS committee). The DMC will include at least 3 physicians and a statistician, none of whom are affiliated with the sponsor. The DMC will review the data approximately every 4 months. At all times the sites and sponsor will remain blinded to treatment allocation. Events to be monitored during the safety review will include at a minimum all serious adverse events (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 Week 104 and open-label extension portions of the study. Investigators and IRBs/IECs will be notified of the outcome of each DMC meeting.

Pharmacokinetics Endpoints and Analysis:

Blood samples will be collected during the study and analyzed to determine serum belimumab concentrations. Serum belimumab concentration data will be used in a population PK analysis, which will be reported separately.

Immunogenicity:

Serum samples for anti-belimumab antibody measurements will be obtained from all randomized subjects before administration of study agent at the baseline visit (Day 0), Week 8, Week 24, Week 52, Week 76 and Week 104. During the 6 month open-label extension, samples will be obtained at Week 24. Additionally, a sample will be collected at the 8-week follow-up visit. For any subject who had a positive antibody response at the 8-week follow-up visit (or last study visit at which immunogenicity was assessed if 8-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or after completion and/or unblinding of the study, whichever is later.

Biological Markers and Autoantibodies:

The following biomarkers will be measured from baseline (Day 0) and at selected timepoints thereafter:

- Autoantibodies: ANA, anti-dsDNA, aCL (IgG, IgM, IgA isotypes), anti-Sm, and anti-C1q
- Serum immunoglobulin isotypes: IgA, IgG, IgM
- Serum complement (C3,C4)
- BLyS protein (baseline only)

In geographies where feasible, the following biological markers will be measured (using FACS analysis) at baseline (Day 0) and at multiple time points thereafter:

- Peripheral B lymphocytes:
  - $CD20^{+}$, $CD20^{+}/27^{+}$ memory, $CD20^{+}/27^{-}$ naïve, $CD20^{+}/69^{+}$ activated, $CD20^{+}/138^{+}$ plasmacytoid, $CD19^{+}/27^{BRIGHT}/38^{BRIGHT}$ SLE subset, $CD19^{+}/CD24^{HIGH}/CD38^{HIGH}$ regulatory B cell and $CD20^{-}/138^{+}$ plasma cells.

Study Calendar:

See Table 6-1, Table 6-2, and Table 6-3 for a calendar of study visits and assessments.

Study Schematic: See Figure 1-1.

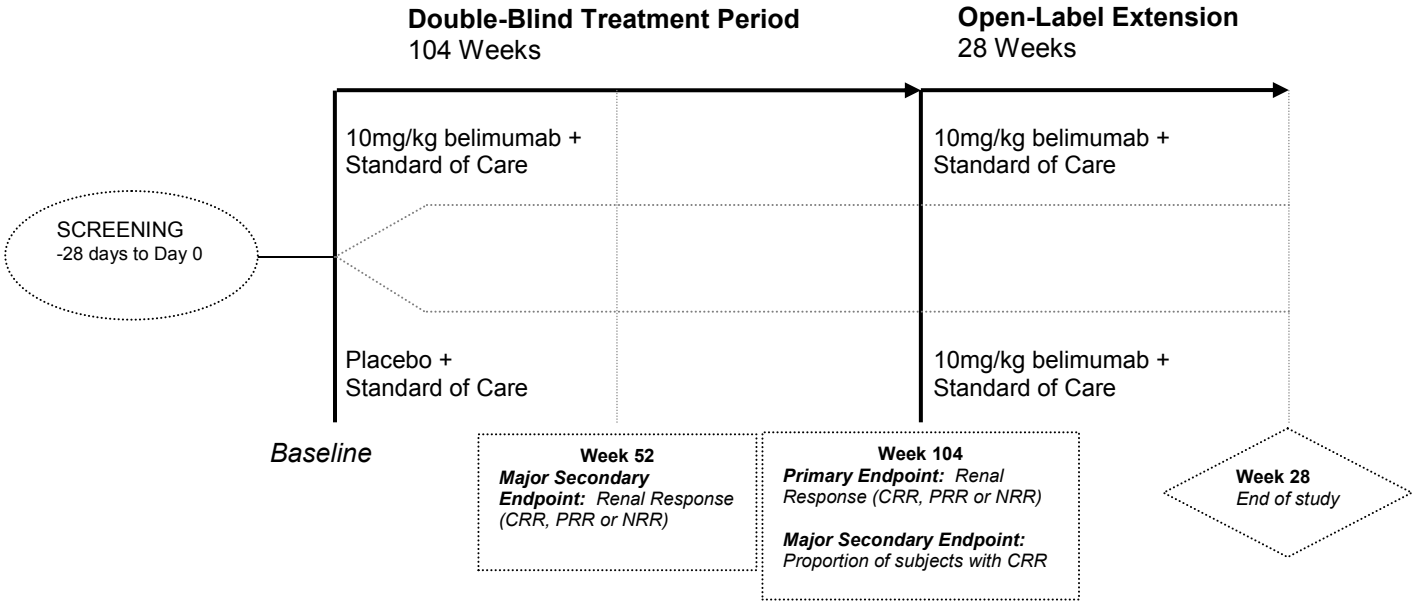

Figure 1-1 Study schematic

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List of Abbreviations

aCL	anticardiolipin
ACE	angiotensin converting enzyme
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ARB	angiotensin receptor antagonists/blockers
Anti-dsDNA	anti-double-stranded DNA
Anti-Sm	anti-Smith antibody
Anti-TNF	anti-Tumor Necrosis Factor
AST	aspartate aminotransferase
AUC	area under the serum drug concentration-time curve
AUCi	area under the curve for an individual subject
AZA	Azathioprine
bid	twice a day
BILAG	British Isles Lupus Assessment Group of SLE Clinics
BLyS	B lymphocyte Stimulator
BR3	BLyS-receptor fusion protein
BUN	blood urea nitrogen
ºC	degrees Celsius
CD	compact disc
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CRR	complete renal response
C-SSRS	Columbia-Suicide Severity Rating Scale
CYC	Cyclophosphamide
CVA	cerebrovascular accident
dL	deciliter
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
dsDNA	double stranded DNA
eCRF	electronic case report form
ECL	electrochemiluminescence
EDC	electronic data capture
ELISA	Enzyme-linked immunosorobent assay
ESRD	end stage renal disease
EU	European Union
FACS	florescence activated cell sorting
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practice

GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GSK	GlaxoSmithKline Pharmaceuticals
HDCS	High dose corticosteroids
Hep-2	Human Epithelial Cell Line 2
HGS	Human Genome Sciences, Inc.
HIV	human immunodeficiency virus
hpf	high power field
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IM	intramuscular
IRB	Institutional Review Board
ISN	International Society for Nephrology
ITT	intention to treat
IU	international unit
IUD	intrauterine device
IV	intravenous
IVIG	intravenous immunoglobulin
IWRS	Interactive Web Response System
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	kilogram
LDH	lactic dehydrogenase
LOCF	last observation carried forward
MDD	major depressive disorder
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MTX	methotrexate
µg	microgram
mg	milligram
mL	milliliter
mmHG	millimeters of mercury
NR	no response
NSAIDs	non-steroidal anti-inflammatory drugs
NWHIC	National Women's Health Information Center
OMHRC	Office of Minority Health Resource Center
PGA	Physician's Global Disease Assessment
PGx	pharmacogenetics
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PRR	partial renal response
PSRHQ	possible suicidality-related history questionnaire
PSRQ	possible suicidality related questionnaire

PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
RPS	Renal Pathology Society
SAE	serious adverse event
SAS	statistical analysis system
SC	subcutaneous
SELENA	Safety of Estrogen in Lupus National Assessment trial
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SOC	System Organ Class
SRI	systemic lupus erythematosus responder index
SWFI	sterile water for injection
TACI-Fc	transmembrane activator attached to Fc portion of an immunoglobulin
tid	three times daily
TNF	tumor necrosis factor
ULN	upper limits of normal
USA	United States of America
USAN/INN	United States adopted names/international nonproprietary name
WBC	white blood cell
WHO	World Health Organization

1 Background

1.1 Disease Background Relevant to Clinical Study

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by autoantibody production and abnormal B lymphocyte function (Pisetsky, 2001). The etiology of SLE is unknown, although genetics, sex hormones, and environmental conditions are thought to play a role (Kotzin, 1996; Pisetsky, 1998; Sobel et al, 1999). This disease is more common in women (~90% of patients) than men (NWHIC, 2003) and more prevalent in African-Americans than Caucasians (OMHRC, 2001; NWHIC, 2003). In the United States the reported prevalence is 100,000 to 500,000 patients with some estimates of 1 million as the incidence increased 2-3 fold between 1950 and 1979. In the European Union (EU), prevalence rates have been reported ranging from 25 to 39 cases per 100,000 persons (Jimenez et al, 2003). In community-based studies among Asians, the prevalence (per 100,000) of SLE ranged from 3.2 to 70.4 (Thumboo and Wee, 2006). The disease onset is generally between the ages of 20 and 40. Patients with SLE have about a 3-fold greater risk of mortality than the general population. Approximately 70% of SLE patients survive 20 years from time of diagnosis (Houssiau et al, 2004).

SLE can lead to arthritis, kidney failure, heart and lung inflammation, central nervous system (CNS) changes, vasculitis, severe skin rash, and blood dyscrasias such as anemia, leukopenia, and thrombocytopenia. The manifestations of SLE vary from patient to patient and it may take many years to render the proper diagnosis. The American College of Rheumatology (ACR) criteria that define a diagnosis of this heterogeneous disease require 4 of 11 criteria that include SLE-associated signs or symptoms, lab abnormalities, and the presence of specific anti-nuclear autoantibodies (Tan et al, 1982).

Approximately 35% of all adult patients with SLE develop clinically significant lupus nephritis and despite improvements in both diagnosis and treatment over the last few decades it remains an indicator of poor prognosis (Gordon et al, 2009; Waldman and Appel, 2006). Manifestations of lupus nephritis include proteinuria, elevations in serum creatinine and the presence of urinary sediment. Alongside these clinical manifestations, morphological changes can be observed in renal biopsy specimens. In 1975 the WHO proposed a classification system for renal biopsies in SLE which was continually revised by them up until 1995. In 2004 updated criteria jointly developed by the International Society of Nephrology and the Renal Pathology Society were published (Weening et al, 2004). Within the 5 overall classes, Classes I and II reflect disease restricted to mesangial abnormalities. Classes III and IV represent either focal (< 50% glomeruli involved - Class III) or diffuse (≥ 50% glomeruli involved - Class IV) segmental or global glomerulonephritis. Class V represents membranous disease with Class VI representing advanced sclerosis. Classes I and II are rarely accompanied by clinical manifestations and there is no activity in Class VI only damage, so therapy has traditionally focused on Classes III-V.

Belimumab (BENLYSTA™) administered IV is approved in the United States (US), Canada, and the European Union (EU) for the treatment of adult patients with active autoantibody-positive SLE who are receiving standard therapy; patients with severe active lupus nephritis

and severe active CNS lupus were excluded, as were patients receiving other biologics and IV cyclophosphamide (Refer to specific country labeling for additional information regarding the approved indication). Approval of IV belimumab for SLE is being sought in other regions of the world.

1.2 Belimumab

1.2.1 Mechanism of Action

Belimumab (also known as LymphoStat-B™; BENLYSTA™) is a B-lymphocyte stimulator (BLyS)-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. Belimumab does not bind B cells directly, but by binding BLyS, belimumab inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

Nonclinical pharmacology, pharmacokinetic (PK), and toxicology data generated with belimumab are provided in the Investigator's Brochure (IB).

1.2.2 Clinical Experience with Belimumab

Belimumab administered as an IV infusion has been studied in SLE patients in 1 Phase 1 trial (LBSL01), 1 Phase 2 randomized, double-blind, placebo-controlled trial (LBSL02) and 2 Phase 3 randomized, double-blind, placebo-controlled trials [BLISS 52 (HGS1006-C1057) and BLISS 76 (HGS1006-C1056)], and in RA patients in a Phase 2 double-blind, placebo-controlled trial (LBRA01).

Phase 3 studies of belimumab in SLE were completed in 2009 and 2010 and formed the basis of the approval of IV belimumab in the US, Canada and the EU. The Phase 3 trials included 1,684 subjects where belimumab 10 mg/kg plus standard therapy demonstrated superiority over placebo plus standard therapy in reduction in disease activity as measured by the SLE responder index (SRI) with an acceptable safety profile. The primary safety population supporting approval also included data from a Phase 2 study in 449 subjects with SLE. Evidence of benefit in other clinical measures such as reductions in disease activity as measured by SELENA SLEDAI, severe flare, and reduced steroid use was also observed. Treatment with belimumab plus standard of care was generally well tolerated, with rates of adverse events (AEs), severe AEs, serious AEs, AEs leading to discontinuation, and serious/severe infections generally comparable to the rates observed in the placebo plus standard of care group. Mortality rates in the controlled clinical trials were low, although numerically higher in the belimumab groups: 0.4% and 0.8% in the placebo and belimumab groups, respectively. Causes of death were as expected in an SLE population with active disease receiving a wide range of standard therapies, such as steroids and immunosuppressants, and included infection, cardiovascular disease, and suicide. Serious infections were observed in 5.2% and 6.0% of subjects receiving placebo and belimumab, respectively. The rate of malignancy (excluding non-melanoma skin cancer) was the same between the placebo and belimumab groups at 0.4%; however as with other immunomodulating agents, the mechanism of action of belimumab could increase the risk for the development of malignancies. Hypersensitivity and infusion reactions were observed.

Anaphylaxis was also observed, though rare (< 1%). Depression-related events, common in patients with SLE, were observed more frequently with belimumab than with placebo; it is unknown if belimumab treatment is associated with an increased risk for these events. The most commonly-reported adverse reactions, occurring in ≥ 5% of patients in clinical trials were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis.

Experience from open-label, long-term continuation trials of belimumab in SLE subjects suggests that prolonged treatment with belimumab remains generally well tolerated, with no apparent increase in the incidence rate of AEs or serious adverse events (SAEs) over time, including important events such as infections and malignancies. The prevalence rate of AEs and SAEs has also remained relatively stable over time. Long term belimumab treatment through 6 years appears to provide sustained improvement in SLE disease activity.

Results of the clinical trials of belimumab administered IV are described in further detail in the Investigator's Brochure.

1.3 Rationale for the Study

Current standard of care treatment for lupus nephritis consists of corticosteroids and immunosuppressants. Several studies have now been conducted in lupus nephritis; however at this time no therapies have been approved for lupus nephritis. In the Euro-lupus trial, a low dose IV cyclophosphamide (CYC) regimen achieved similar clinical results with respect to treatment failures, renal remission and renal flares when compared to a high dose IV CYC regimen (Houssiau et al, 2002). A recent systematic review of recent trials in lupus nephritis concluded that MMF is as effective as CYC in inducing disease remission (Touma et al, 2011).

Belimumab treatment at a dose of 10 mg/kg in combination with standard SLE therapy demonstrated a statistically significant and clinically meaningful reduction in SLE disease activity vs placebo plus standard SLE therapy at week 52 in 2 Phase 3 clinical studies (C1056/BLISS76 and C1057/BLISS52) in subjects with active, autoantibody-positive SLE. While the 2 Phase 3 studies did explore the effect of belimumab on individual organ systems, these findings were limited for the renal organ domain as subjects were excluded if they had severe active lupus nephritis. However, 267 subjects (16%) included in the Phase 3 trials had renal involvement by SELENA SLEDAI (comprising hematuria, proteinuria, pyruia and/or urinary casts). In a post-hoc analysis of the pooled data (Table 1-1), there were trends towards SELENA SLEDAI renal organ domain improvement, especially in the subgroup of subjects who were anti-dsDNA positive and had low C3 and/or low C4 at baseline. There were favorable trends of greater reduction in proteinuria, hematuria, pyuria, and lower renal flare rate in the belimumab treatment groups versus placebo. Understanding whether belimumab plus standard of care can reduce the disease activity in subjects with active lupus nephritis subjects is of interest to prescribing physicians and health authorities.

Table 1-1 Renal Endpoints at Week 52-Phase 3 Trials

	Phase 3 Studies Pooled		
	Placebo N = 562	**1 mg/kg N = 559**	**10 mg/kg N = 563**
SELENA SLEDAI Renal Improvement[1]			
In patients with the following at baseline:			
Renal involvement[2]	39/92 (42.4%)	43/90 (47.8%)	42/85 (49.4%)
Renal involvement + high activity[3]	37/87 (42.5%)	39/86 (45.3%)	42/82 (51.2%)
Renal involvement + anti-dsDNA+low C[4]	21/62 (33.9%)	24/60 (40.0%)	28/60 (46.7%)
Proteinuria	(n = 116)	(n = 110)	(n = 112)
Median % reduction[5]	27.5	48.3	39.1
Renal Flare			
Subjects with renal flare[6]	16 (2.8%)	14 (2.5%)	8 (1.4%)
Relevant Biomarkers			
Anti-dsDNA[7]			
Positive to Negative	19/280 (6.8%)	47/314 (15.0%)	50/313 (16.0%)
C3[8]			
Low to Normal/High	30/176 (17.0%)	51/193 (26.4%)	77/202 (38.1%)
C4[9]			
Low to Normal/High	40/218 (18.3%)	86/246 (35.0%)	115/259 (44.4%)

1 SELENA SLEDAI renal domain includes hematuria, proteinuria, pyuria, and urinary casts.
2 In subjects with renal involvement at baseline (dropout=failure).
3 In subjects with renal involvement and SELENA SLEDAI score ≥ 7 at baseline (dropout=failure).
4 In subjects with renal involvement and anti-dsDNA+/low complement at baseline (dropout=failure).
5 In subjects with > 0.5 g at baseline (LOCF).
6 Censored at last assessment or start of rescue medications.
7 Anti-dsDNA: Positive (≥ 30 IU/mL); Negative (< 30 IU/mL).
8 C3: Normal/High (≥ 900 mg/L); Low (< 900 mg/L).
9 C4: Normal/High (≥ 16 mg/dL); Low (< 16 mg/dL).

TE24.1, TE26.1, TE26.2 (C1056); TE24.1, TE26.1, TE26.2 (C1057);
TA46.7, TAC790, TAC340, TAC397, TA1 (ISE)

In the 2 Phase 3 studies, several clinical measures of improvement including the primary efficacy endpoint at Week 52 (SLE responder index or SRI), SELENA SLEDAI reductions, severe flare risk reduction, and complement normalization generally favored the 10 mg/kg dose. Trends toward clinically significant steroid reduction were present for both doses. Additionally, there appeared to be a greater dose response in subjects with high disease and serological activity than in subjects with lower activity. There was no apparent dose-response in the safety profile of belimumab, with both doses being generally well-tolerated, further supporting the selection of 10 mg/kg belimumab as the recommended dose in combination with standard therapies.

The current study is designed to evaluate the efficacy (ie, induction and maintenance of renal remission) and safety of 10 mg/kg belimumab administered IV in combination with standard of care (including MMF, CYC, corticosteroids and AZA) in subjects with active lupus nephritis.

2 Study Objectives

- To evaluate the efficacy of belimumab in combination with standard of care in adult subjects with lupus nephritis Class III, IV or V using the 2003 ISN/RPS criteria.
- To assess the safety and tolerability of belimumab plus standard of care versus placebo plus standard of care in adult subjects with lupus nephritis Class III, IV or V using the 2003 ISN/RPS criteria.

3 Study Design

3.1 Basic Design Characteristics

This is a Phase 3, multi-center, multi-national, randomized, double-blind, placebo controlled study to evaluate the efficacy and safety of intravenous belimumab 10 mg/kg plus standard of care compared to placebo plus standard of care in adult subjects with active lupus nephritis.

Subjects who meet the eligibility criteria during screening will be randomized to 1 of 2 treatment groups in a 1:1 ratio: 10 mg/kg belimumab plus standard of care or placebo plus standard of care. The randomization of all eligible subjects will be stratified by their induction regimen (high dose cortiocsteroids [HDCS] plus CYC vs HDCS plus MMF) and race (black race vs other). Subjects will be dosed with study agent on Days 0 (baseline), 14, 28 and then every 28 days through 100 weeks with a final evaluation for the double-blind treatment period at 104 weeks. Approximately 464 lupus nephritis subjects will be randomized with a target of 232 subjects in the belimumab treatment group and 232 in the placebo group. All subjects will receive background therapy consisting of one of the following standard of care regimens:

- High Dose Corticosteroids (HDCS) + Cyclophosphamide (CYC) for induction therapy followed by AZA for maintenance therapy

  OR

- HDCS + Mycophenolate Mofetil (MMF) for induction followed by MMF for maintenance therapy

The standard of care medications are described in Section 5.5.1.

All subjects will start the above induction therapy within 14 days prior to the baseline (Day 0) visit. This will allow subjects to be screened and potentially enrolled so they will not be excluded on the basis of necessary acute management. If an induction regimen has been received within 6 months prior to the screening visit, the subject will be excluded. The

primary efficacy endpoint of a renal response will be a composite endpoint including changes in urinary sediment, proteinuria, and renal function at Week 104. For the renal function assessments at baseline, Week 24, 48, 52, 76, 100 and 104, the glomerular filtration rate (GFR) will be based on the mean value of 2 contiguous 24 hour urine collections and 2 serum creatinine measurements (first serum creatinine collected at initial visit and the second sample taken 3 days later at the follow-up visit). Subjects will be provided with the materials for collecting the two 24 hour urine collections beginning the next morning following their initial clinic visit. On the third day following the initial visit, subjects will return to the clinic for the second serum creatinine sample. For all other study visits, GFR will be estimated using the simplified MDRD formula and the urinary protein: urinary creatinine will be used for proteinuria.

For the urinary sediment assessments, both menstrual cycles and genitourinary tract infections may be confounders. The urine collection may be postponed up to 14 days at the investigators discretion if menstrual bleeding or a genitourinary tract infection is present at anytime during the 24 hour urine collection.

Renal response will be measured as complete, partial, or no response based on study defined criteria (see Section 8.5). Week 104 renal response will be defined by a response at Week 100 that is confirmed by a repeat measurement at Week 104.

All subjects who discontinue treatment during the double-blind period (for reasons other than receipt of prohibited medications or doses of medications that result in treatment-failure designation or withdrawal of consent) should return for the scheduled visits through Week 104. For subjects who discontinue study treatment due to receipt of prohibited medications, an Exit visit should be completed approximately 4 weeks after the last dose of study agent and a Follow-up visit approximately 8 weeks after the last dose of study agent.

In the event that a subject withdraws consent from the study, an attempt should be made to obtain consent for mortality status at Week 104. Any subject that withdraws consent for use and disclosure of research-related health information will be considered withdrawn from the study and not followed for mortality.

Subjects who successfully complete the initial 104-week double blind period may enter into a 6-month open-label extension. The Week 104 visit of the double-blind period will serve as the Day 0 visit for subjects entering the 6-month open-label extension. In the open-label extension, all subjects will receive 10 mg/kg belimumab every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the last dose). The first dose on the open-label extension will be given at the Week 104 visit of the double-blind period following the completion of all Week 104 assessments. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety as per the study calendar (see Table 6-3). Subjects who complete the 104-week double-blind period, but do not enter the open label extension will be required to return for an additional follow up visit 8 weeks after the last dose of study agent. All subjects who enter the open-label extension period and withdraw early will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent.

At the end of the 6-month open-label extension period, subjects who wish to continue treatment may do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may continue to receive belimumab under this protocol until belimumab becomes commercially available.

4 Inclusion and Exclusion Criteria

4.1 Inclusion Criteria

Subjects enrolled in the study must meet the following inclusion criteria:

1. Males or females at least 18 years of age.
2. Have a clinical diagnosis of SLE according to the American College of Rheumatology (ACR) criteria (Appendix 1).
3. Have active, biopsy-proven proliferative lupus nephritis Class III or IV (excluding Class III(C), IV-S(C) and IV-g(C)), either with or without the presence of Class V, or pure Class V membranoususing the 2003 ISN/RPS criteria (Appendix 2); the biopsy must be performed in the 6 months prior to baseline (Day 0). Whenever possible, a tissue sample from the renal biopsy used to qualify the subject will be collected and sent to a central reading center; however, the tissue sample will not be shipped prior to nor be used for the purposes of randomization.
4. Have unequivocally positive ANA test results defined as an ANA titer ≥ 1:80 (based on Hep-2 immunofluorescence assay) and/or a positive anti-dsDNA (≥ 30 IU/mL based on ELISA assay) serum antibody test at the screening visit based on the study's central laboratory results.
5. Have documentation of active renal disease at screening requiring initiation of induction therapy with high dose corticosteroids (HDCS) with either IV cyclophosphamide (CYC) or mycophenolate mofetil (MMF) or other oral forms of mycophenolate. Induction therapy should be started no more than 14 days prior to the baseline visit (Day 0). The following factors will be used to define active renal disease:
   - Urinary protein:creatinine ratio of ≥ 1.0 AND active urinary sediment as defined by ≥ at least 1 of the following (in absence of menses and genitourinary tract infection).
     - > 5 red blood cell (RBC)/high power field (hpf) (or above the laboratory reference range)
     - > 5 white blood cell (WBC)/hpf (or above the laboratory reference range).
     - Presence of cellular casts (RBC or WBC).
   - Subjects without active urinary sediment are eligible if they meet at least 1 of the following criteria:
     - Have a confirmatory biopsy performed within 3 months prior to the baseline visit meeting the criteria outlined in criterion 3.
     - Have proteinuria ≥ 3.5 grams/day.

6. A female subject is eligible to enter the study if she is:
   - Not pregnant or nursing;
   - Of non-childbearing potential (ie, women who had a hysterectomy, are postmenopausal which is defined as 1 year without menses, have both ovaries surgically removed or have current documented tubal ligation or any other permanent female sterilization procedure); or
   - Of childbearing potential (ie, women with functional ovaries and no documented impairment of oviductal or uterine function that would cause sterility). This category includes women with oligomenorrhoea [even severe], women who are perimenopausal or have just begun to menstruate. These women must have a negative serum pregnancy test at screening, and agree to 1 of the following:
     - Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent; or
     - Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during study and 16 weeks after the last dose of study agent:
       - Implants of levonorgestrel or etonogestrel;
       - Ethinyl estradiol/Etonogestrel vaginal ring;
       - Injectable progesterone;
       - Any intrauterine device (IUD) with a documented failure rate of less than 1% per year;
       - Oral contraceptives (either combined or progesterone only);
       - Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) with spermidical foam/gel/film/cream/suppository;
       - Transdermal contraceptive patch;
       - Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for the female subject.
7. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information) and comply with the study protocol procedures (including required study visits).

4.2 Exclusion Criteria

Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Subjects who have previously failed induction therapy with both CYC and MMF (or other forms of mycophenolate) based on the investigator's opinion. If a subject has failed only 1 of the 2 therapies for induction, they may be eligible for study inclusion if they are newly initiating the other induction therapy (ie, a subject who failed MMF is eligible if newly initiating induction therapy with CYC or a subject who failed CYC is eligible if newly initiating induction therapy with MMF).

2. Subjects who have previously received an induction therapy within 6 months prior to the screening visit.
3. Subjects who receive CYC whose pre-induction leukocyte count is Grade 3 or 4 based on the Adverse Event Severity Grading Tables (Appendix 7).
4. Known hypersensitivity or contraindication to any drug products or any component of these drug products they plan to receive (eg, CYC, MMF, AZA, corticosteroids).
5. Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.
6. Have received treatment with belimumab at anytime.
7. Received the following within 364 days of baseline (Day 0):
   - Nitrogen mustard
   - Chlorambucil
   - Vincristine
   - Procarbazine
   - Etoposide
   - Abatacept
   - Treatment with any B cell targeted therapy (eg, rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI-Fc, or LY2127399 [anti-BAFF])
   - A biologic investigational agent (eg, abetimus sodium, anti-CD40L antibody [BG9588/ IDEC-131]). Investigational agent applies to any drug not approved for sale in the country in which it is being used.
8. Received any of the following within 90 days of baseline (Day 0):
   - Anti-TNF therapy (eg, adalimumab, etanercept, infliximab)
   - Interleukin-1 receptor antagonist (anakinra).
   - Intravenous immunoglobulin (IVIG).
   - Plasmapheresis.
9. Received a non-biological investigational agent within 60 days of baseline (Day 0).
10. Received a live vaccine within 30 days of baseline (Day 0).
11. 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 baseline (Day 0).
12. Have a history of a major organ transplant (eg, heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant or are due to receive transplantation.
13. Subjects who have been on dialysis within 364 days of baseline (Day 0).
14. An estimated glomerular filtration rate < 30 ml/min at the screening visit (using the simplified Modification of Diet in Renal Disease [MDRD] equation).
15. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to SLE (ie, cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, 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 a planned surgical procedure or a history of any other medical disease (eg, cardiopulmonary), laboratory abnormality, or condition (eg, poor venous access) that, in the opinion of the principal investigator, makes the subject unsuitable for the study.

17. Have a history of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix.
18. Have required management of acute or chronic infections, as follows:
    - Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
    - Hospitalization for treatment of infection within 60 days of baseline (Day 0).
    - Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of baseline (Day 0).
19. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to baseline (Day 0).
20. Have a historically positive test or test positive at screening for HIV antibody, hepatitis B surface antigen, or hepatitis C antibody.
21. Have an IgA deficiency (IgA level < 10 mg/dL).
22. Have a Grade 3 or greater laboratory abnormality based on the Adverse Event Severity Grading Tables (Appendix 7) except for the following that are allowed:
    - Urinalysis (eg, proteinuria)
    - Hematuria
    - Pyuria
    - Casts
    - Hypoalbuminemia due to lupus nephritis.
    - Stable Grade 3 prothrombin time (PT) secondary to warfarin treatment.
    - Stable Grade 3 partial thromboplastin time (PTT) due to lupus anticoagulant and not related to liver disease or anti-coagulant therapy.
    - Stable Grade 3 gamma glutamyl transferase (GGT) elevation due to lupus hepatitis, and not related to alcoholic liver disease, uncontrolled diabetes or viral hepatitis. If present, any abnormalities in the ALT and/or AST must be ≤ Grade 2.
    - Stable Grade 3 neutropenia or stable Grade 3 white blood cell count. (Note that WBC count should be obtained immediately prior to starting induction therapy. If immediate pre-induction WBC is not available, a WBC count obtained within 28 days prior to induction may be used).
23. Subjects who 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 (Appendix 8) in the last 2 months or who in the investigator's opinion, pose a significant suicide risk.

5 Study Treatment Regimen

5.1 Study Agent Name and Formulation

The common name of the study agent is BENLYSTA™. The generic (USAN/INN) name is belimumab.

Belimumab is a recombinant, human, IgG1λ monoclonal antibody specific for soluble human B lymphocyte stimulator (BLyS, also referred to as BAFF and TNFSF13B). Belimumab has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

Belimumab drug product is provided as a sterile, lyophilized product. Upon reconstitution with sterile water for injection (SWFI), each vial will contain 80 mg/mL belimumab in 0.16 mg/mL citric acid, 2.7 mg/mL sodium citrate, 80 mg/mL sucrose, 0.4 mg/mL polysorbate 80, pH 6.5. Each lyophilized vial is single use.

The placebo control is prepared as a sterile and lyophilized product. Upon reconstitution with 4.8 mL SWFI, each vial will contain 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 80 mg/mL sucrose, 0.4 mg/mL polysorbate 80, pH 6.5. Each lyophilized vial is single use.

5.2 Packaging, Labeling, Preparation, and Storage

Belimumab will be supplied in a 20 mL vial containing 400 mg belimumab (deliverable).

Placebo control will be supplied in a 20 mL vial.

Lyophilized belimumab and placebo should be stored at 2-8°C. After reconstitution and dilution in normal saline, the material is stable for up to 8 hours at 2-8°C, or at room temperature. Refer to the Pharmacy Manual for detailed instructions on the preparation, administration, and storage of study agent.

The 400 mg single use vial of study agent will be reconstituted with 4.8 mL SWFI, to yield a final concentration of 80 mg/mL of belimumab. Placebo will be reconstituted with 4.8 mL SWFI.

In addition to any country-specific requirements, the study agent label will contain, at a minimum, the following information:

- Product name
- Concentration
- Lot number
- Storage conditions
- Investigational drug statement
- Manufacturer’s name and address

The calculated dose of study agent to be administered to the subject is determined in milligrams (mg) by the assigned treatment group and the subject's body weight in kilograms (kg) at baseline (Day 0) of this study. If a subject's weight increases or decreases by more than 5% from their baseline (Day 0) weight on this study, the current weight should be used to calculate the dose of study agent administered.

The reconstituted study agent will be diluted in 250 mL normal saline for IV infusion. An amount of normal saline, equal to the calculated amount of product to be added (see Section 5.1), should be removed from the infusion bag prior to adding the product. After adding the reconstituted product, gently invert the bag to mix the solution.

Belimumab and placebo will be supplied as open-label vials and 3rd party unblinding will be employed. The study agent will be reconstituted and diluted by the unblinded site pharmacist or designee, independent of the study (person responsible for receiving and dispensing study agent). Except for a limited number of safety oversight personnel, all other site personnel, the subject, the sponsor and contract research organization (CRO) will remain blinded to the study agent received and to certain biomarkers and pharmacodynamic laboratory results (see Section 6.12). Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

Study agent inventory/accountability forms will be examined and reconciled by the unblinded monitor or designee as long as the study is blinded. After the end of the study all used and unused study agent must be accounted for on a study agent accountability form provided to the investigator by the sponsor, or its designee.

Refer to the Pharmacy Manual for more details regarding storage, handling, and drug accountability.

5.3 Dose, Route of Administration, and Schedule

The treatment groups include one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving standard of care therapy (as described in Section 5.5.1). All study agent treatments will be administered intravenously over 1 hour. Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days days thereafter through 100 weeks of double-blind treatment. Following the final double-blind visit at Week 104, subjects who will have the option to continue in the 6-month open-label extension period (with first dose given at Week 104 visit).

Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion. Antihistamine H2-receptor antagonists (eg, ranitidine) are also permitted.

Study agent should be administered by Investigators/site personnel prepared to manage infusion reactions and anaphylaxis. The infusion rate may be slowed or interrupted if the subject develops an infusion reaction. Investigators/site personnel should be aware of the risk of hypersensitivity reactions, which may present as infusion reaction, and monitor subjects closely. In the event of a serious reaction, study agent administration must be discontinued immediately and the appropriate medical therapy administered. Subjects should be monitored

during and for an appropriate period of time after infusion according to study sites' guidelines or standard operating procedure for IV infusions. This may include, but is not limited to, monitoring vital signs and observing for any untoward reactions. Subjects should also be informed of the signs and symptoms of a hypersensitivity reaction and instructed to seek medical care should a reaction occur.

5.4 Alteration of Dose/Schedule Due to Toxicity

The dose of study agent administered may not be altered. The rate of infusion may be slowed or interrupted if the subject appears to develop signs of adverse reaction or infusion-associated symptoms. At later visits, these subjects may continue to be infused over a longer infusion period at the investigator's clinical discretion.

If a subject experiences a clinically significant AE that the investigator believes may be definitely, possibly or probably related to study agent and could potentially be exacerbated by the next dose, the investigator may delay the dose by up to 2 weeks or withhold 1 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 should be discontinued.

If a subject experiences a clinically significant, potentially *life-threatening* (Grade 4) AE that the investigator believes may be definitely, possibly or probably related to study agent, then treatment with study agent will be discontinued. The subject should be withdrawn from the study agent, and followed at regularly scheduled study visits as specified by protocol and also until resolution of the AE(s) (whichever is longer). All subjects should be monitored closely for infection. Increased vigilance for infection is recommended in subjects who experience IgG levels < 250 mg/dL, especially for prolonged periods; clinical judgment should be applied with respect to the appropriateness of continuing study therapy in these subjects. The Medical Monitor must be consulted before administering subsequent doses of study agent in subjects with IgG levels < 250 mg/dL. Study agent will be discontinued in subjects with IgG levels < 250 mg/dL that are associated with a severe or serious infection.

5.5 Concurrent Medications

This section reviews medications which are allowed during the course of the study provided the guidelines below are followed. Anytime the concurrent medication guidelines are not followed, the subject will have study agent discontinued and will be considered a treatment failure (non-responder).

Whenever possible, a complete disease activity assessment (SELENA SLEDAI, SLE Flare Index and PGA) and laboratory assessments (hematology, chemistry, urinalysis, anti-dsDNA, and complement) should be performed to document renal flare prior to instituting treatment that results in treatment failure designation.

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

5.5.1 Standard of Care Medication

This section reviews the required induction and maintenance standard of care regimens. All subjects will receive background standard of care therapy consisting of either CYC plus HDCS for induction plus AZA for maintenance or MMF plus HDCS for induction followed by MMF for maintenance. Each investigator must refer to the country-specific label for each required medication and heed appropriate warnings and precautions.

Cyclophosphamide and Azathioprine

Cyclophosphamide (CYC) used for induction therapy will consist of 500 mg by IV infusion every 2 weeks for 6 infusions. Adjustments may be made for tolerability issues. For the maintenance period, AZA will be started 2 weeks after the last dose of CYC with a target dose of 2 mg/kg/day (not to exceed 200 mg/day) until study end. A prescribed dose greater than 2 mg/kg/day is prohibited and considered to constitute treatment failure. It is recommended that dosing commence at 50 mg/day and increase by no more than 50 mg/day every week until the target dose is achieved. Adjustments may be made for tolerability issues. Subjects who develop Grade 3 or 4 leucopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above a switch to MMF will be permitted. The use of mesna and/or leuprolide (leuprorelin) is permitted with CYC dosing in accordance with the usual practice of the investigator.

Mycophenolate Mofetil

MMF used for induction and maintenance therapy is recommended at a dose from 1-3 g/day orally through study end. Dosing of MMF will start at 0.5 g twice a day (bid) for the first week, increase to 1 g bid for the second week, and then 1.5 g bid for the third and subsequent weeks. MMF will be taken morning and evening, before meals, with a glass of water. If tolerability issues are experienced with bid dosing, subjects may receive 1 g 3x/day (tid). If tid dosing not tolerated, the MMF dose may be reduced to as low as 1g/day. Subjects who develop a grade 3 or 4 neutropenia, following initiation of MMF will be permitted to reduce the dose to no less than 1g/day. A prescribed dose greater than 3 g/day is prohibited and considered to constitute treatment failure.

After 6 months of therapy, the dose of MMF may be reduced to 1 g/day or subjects may be switched to AZA (target dose 2 mg/kg) for tolerability reasons.

Mycophenolate sodium may be used in lieu of MMF for induction and maintenance therapy. A dose from 720 mg/day to 2160 mg/day orally is recommended. A dose greater than 2160 mg/day is prohibited and considered to constitute treatment failure.

The use of IV forms of mycophenolate is prohibited.

High Dose Corticosteroids

At the outset of the study, all subjects must be on a daily corticosteroid regimen.

The study recommended corticosteroid regimen includes 0-3 IV pulses of methylprednisolone 500 mg-1000 mg/pulse followed by an oral prednisone dose of up to 60 mg/day. It is recommended that oral corticosteroids be tapered according to the Table 5-1. If necessary, it may take longer than 12 weeks to complete the taper.

Note: All subjects must be receiving 10 mg of prednisone/day or less by Week 24 or they will be considered a treatment failure.

Table 5-1 Recommended oral prednisone taper regimen

Study Week	Reduced Dose (mg/day)
0	60
2	50
3	45
4	40
5	35
6	30
7	25
8	20
9	17.5
10	15
11	12.5
12	10

5.5.2 Immunosuppressives

The primary objective of this trial is to evaluate the efficacy of belimumab plus standard of care to reduce lupus nephritis disease activity. Other immunosuppressives (eg, Methotrexate [MTX]) will be allowed provided these are started prior to baseline and meet eligibility criteria. Dose alterations during the trial of these agents are permitted. Subjects who newly initiate immunosuppressives (with the exception of topical agents) after the baseline visit outside the induction regimen will be considered treatment failures.

5.5.3 Angiotension Pathway Antihypertensives

Investigators are encouraged to consider whether the subject might benefit from angiotensin pathway antihypertensive agents (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor antagonists/blockers [ARBs]), or a combination therapy that includes these agents, to treat hypertension or SLE-related nephropathy. ACE inhibitor and ARB use is allowed in this study as described in this section. Since these medications may confound efficacy assessment by mimicking renal deterioration (eg, increased serum creatinine) or improving renal function (eg, beneficial remodeling of renal parenchyma), the following guidelines should be applied.

- Starting a new angiotensin pathway antihypertensive (ACE inhibitor, angiotensin receptor blocker) treatment after the Week 24 visit will cause the subject to be declared a treatment failure.
- An angiotensin pathway antihypertensive will be considered new if the subject did not receive an angiotensin pathway antihypertensive at any time during the Day 0 to Week 24 treatment interval.
- An angiotensin pathway antihypertensive may be replaced with another angiotensin pathway antihypertensive at any time during the study.
- Titration of dose to obtain therapeutic effect on blood pressure is allowed.
- Initiation of new antihypertensive agents other than ACE inhibitors or ARBs is permitted.

5.5.4 Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Aspirin

The use of NSAIDs is not recommended during the study, although use would not constitute a treatment failure

5.5.5 Corticosteroids

5.5.5.1 Systemic Corticosteroids for Non-renal SLE-related Disease Activity

All subjects should be receiving a corticosteroid dose of 10 mg or less by Week 24. Those who cannot be tapered to 10 mg or less by Week 24 will be declared treatment failures. No corticosteroid rescue treatment will be allowed from Week 76-104. Outside of this window, there will be a limited number of corticosteroid rescue treatments allowed if clinically indicated for non-renal SLE-related disease activity as outlined below.

- Up to 2 corticosteroid rescue treatments will be allowed.
- At least a 3-month interval is required between each treatment.
- Each treatment should be no longer than 7 days in duration with the steroid dose returning to ≤ 10 mg/day or no more than 5 mg above their Week 24 dose (whichever is higher) by Day 7.
- Up to 20 mg/day (prednisone or prednisone equivalent) is permitted.
- There can be no concurrent worsening of renal disease.

Any subjects who require corticosteroid rescue treatment exceeding the above criteria or who are unable to return to a dose no more than ≤ 10 mg/day or no more than 5 mg above their Week 24 dose (whichever is higher) will be considered treatment failures. Additionally, any subjects who have not returned to ≤ 10 mg/day by Week 76 will be considered treatment failures.

5.5.5.2 Systemic Corticosteroids for Renal SLE-related Disease Activity

All subjects should be receiving a corticosteroid dose of 10 mg or less by Week 24. Those who cannot be tapered to 10 mg or less by Week 24 will be declared treatment failures.

The use of corticosteroids at a dose of > 15 mg/day for treatment of a renal flare (with or without concurrent non-renal SLE disease activity) is prohibited and the subject would be considered a treatment failure.

5.5.5.3 Systemic Corticosteroids for Non-SLE Disease Activity

No corticosteroid rescue treatment will be allowed from Week 76-104. Outside of this window, there will be a limited number of corticosteroid treatments allowed if clinically indicated for the treatment of non-SLE disease activity (eg, allergic reaction).

- Up to 3 corticosteroid treatments will be allowed.
- At least a 3 month interval is required between each treatment.
- Each treatment should be no longer than 3 days in duration with the steroid dose returning to ≤ 10 mg/day or no more than 5 mg above their Week 24 dose (whichever is higher) by Day 7.
- Up to 100 mg/day (prednisone or prednisone equivalent) will be permitted.

Any subjects who require corticosteroid rescue treatment exceeding the above criteria or who are unable to return to a dose no more than ≤ 10 mg/day or no more than 5 mg above their Week 24 dose (whichever is higher) will be considered treatment failures. Additionally, any subjects who have not returned to ≤ 10 mg/day by Week 76 will be considered treatment failures.

5.5.5.4 Intraarticular Injections

Intraarticular injections will be allowed as clinically indicated. However, no intraarticular corticosteroid injections should be given from Week 96-104 although this use would not constitute a treatment failure

5.5.5.5 Inhaled and Topical Corticosteroids

Inhaled and topical steroids are allowed throughout the course of the study.

5.6 Prohibited Medications and Non-Drug Therapies

Subjects who start the prohibited medications or therapies listed below at any time during the study will be considered treatment failures for analysis (ie, non-responders) and must be withdrawn from study agent and return for required exit and follow-up visits. The following medications and therapies are prohibited at any time during the study:

- New immunosuppressant agents (other than described in Section 5.5.1 as part of the induction and maintenance regimens).
- Corticosteroid use outside of the limits described in Section 5.5.5.
- 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.
- Anti-TNF therapy (eg, adalimumab, etanercept, infliximab).

- Other biologics (eg, rituximab, abatacept, interleukin-1 receptor antagonist [anakinra]).
- Intravenous immunoglobulin (IVIG).
- Plasmapheresis.

Whenever possible, a complete disease activity assessment (SELENA SLEDAI, PGA, and laboratory assessments (hematology, chemistry, urinalysis, anti-dsDNA, and complement) should be performed to document renal flare prior to instituting treatment that results in treatment failure designation as defined in Sections 5.5 and 5.6.

5.6.1.1 Live Vaccines

Live vaccines are not permitted in the study. Subjects who require a live vaccine during the study should have study agent discontinued prior to receiving the live vaccine. These subjects should be followed according to the study protocol until the study endpoint is reached (Week 104 or until receipt of a prohibited medication or dose resulting in treatment failure designation).

6 Study Procedures

The nature of potential risks and benefits associated with participation in the study will be explained to all potential study subjects. Written informed consent (including consent for the use and disclosure of research-related health information) must be obtained before the subject can begin any screening procedures that are not considered part of standard patient care.

Subjects participating in the pharmacogenetics (PGx) research portion of the protocol (Appendix 6) must sign the PGx informed consent prior to any PGx samples being drawn from the subject.

Refer to the Study Calendar (Table 6-1, Table 6-2, and Table 6-3), Study Procedures Manual and Central Laboratory Manual for additional information.

6.1 Screening Procedures (Day -28 to Day 0)

The following assessments are required at screening:

- Demographics.
- Medical history.
- Complete physical examination (including vital signs).
- Confirm diagnosis of SLE disease (based on ACR criteria) by reviewing previously documented clinical records (see Appendix 1).
- Record concurrent medications.
- Blood samples for: (see Appendix 5 – Laboratory Tests)
  - Hematology.
  - Modified Chem 20 (non-fasting).

- Serum pregnancy test - for all women with an intact uterus, unless exempted from pregnancy testing (ie, of non-childbearing potential - women who had a hysterectomy, are post-menopausal which is defined as 1 year without menses, have both ovaries surgically removed or have current documented tubal ligation or any other permanent female sterilization procedure).
- Autoantibodies (ANA and anti-dsDNA).
- Biological Markers (Complement C3, C4).
- Serum Immunoglobulin isotypes (IgG, IgM, IgA).
- HIV antibody, hepatitis B surface antigen, and hepatitis C antibody testing.
- PT/PTT

- Urine sample for:
  - Urinary protein: urinary creatinine ratio.
  - Locally performed urinary microscopy and routine urinalysis.
- Renal biopsy result (should be from a renal biopsy obtained in the 6 months prior to baseline (Day 0). Whenever possible, a tissue sample from the renal biopsy used to qualify the subject will be collected and sent to a central reading center; however, the tissue sample will not be shipped prior to nor be used for the purposes of randomization.
- Suicidality assessment by using the Columbia-Suicide Severity Rating Scale (C-SSRS) Screening assessment form (see Section 7.6 and Appendix 8).
- Confirm subject meets study entry criteria.

6.2 Study Enrollment Procedures

Subjects who have undergone all screening procedures and have met the entry criteria will be enrolled into the study and assigned to treatment by Interactive Web Response System (IWRS). Subjects will be randomized in a 1:1 ratio to treatment with either 10 mg/kg belimumab plus standard of care or placebo plus standard of care. Randomization of all eligible subjects will be stratified by their induction regimen (HDCS plus CYC vs HDCS plus MMF) and race (black race vs other). There is race stratification in this study because race may be an important factor related to outcomes in patients with lupus nephritis. Race should be self-designated.

6.3 Double-Blind Treatment Period

Subjects will be evaluated at the study site during the scheduled study visits as outlined in the Study Calendar (Table 6-1 and Table 6-2). Time windows are provided for each study visit to allow flexibility in site and subject scheduling. All study visits should occur within the visit window of the scheduled study visit.

At baseline (Day 0), the subject will be randomized and receive the first dose of study agent. Visits to the study sites for clinical evaluation, disease activity assessment, and laboratory sampling will occur every 28 days (calculated from the Day 0 dose) through Week 104. All efforts should be made to retain subjects on schedule, based on the date of their Day 0 dose. During the double-blind treatment period, study agent is administered at every

scheduled visit through Week 100. The final efficacy evaluation for the double-blind portion of the study will occur at Week 104.

Subjects who complete the double-blind period through Week 104 will be given the option to receive belimumab in the 6-month open-label extension.

- Subjects who complete the 104-week double-blind period, but do not enter the open label extension, will not have study agent administered at Week 104. Assessments should be completed for the Week 104/Exit visit, and then the subject should return in 4 weeks for the Follow-up Visit.
- Subjects who wish to continue in the open-label extension, will have study agent administered at the Week 104 visit after all Week 104 assessments are performed (refer to Section 6.4 below).

All subjects who discontinue treatment during the double-blind period (for reasons other than receipt of prohibited medications or doses of medications that result in treatment-failure designation or withdrawal of consent) should return for the scheduled visits through Week 104. At a minimum, survival status should be collected at Week 104.

For subjects who discontinue study treatment due to receipt of prohibited medications or doses of medications that result in treatment failure designation, and subjects who discontinue treatment and do not return for scheduled visits through Week 104, an Exit visit should be completed approximately 4 weeks after the last dose of study agent and a Follow-up visit completed approximately 8 weeks after the last dose of study agent.

In the event that a subject withdraws consent during the double-blind treatment period, an attempt should be made at the time of consent withdrawal to obtain consent to collect survival status at Week 104. Any subject that withdraws consent for use and disclosure of research-related health information will be considered withdrawn from the study and not followed for mortality.

Table 6-1 Study Calendar - Double-Blind Treatment Period (Screen-Week 52)

	Screening	Baseline	Double-Blind Treatment Period																	
Study Day	**-28 days**	**0**		**14±3 days**	**28±3 days**	**56±7 days**	**84± 7 days**	**112±7 days**	**140± 7 days**	**168± 7 days**		**196± 7 days**	**224± 7days**	**252± 7days**	**280± 7days**	**308± 7days**	**336± 7days**		**364± 7days**	
Study Week	**Wk -4**	**Wk 0**	**Wk 0 + 3d**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**WK 20**	**Wk 24**	**Wk 24 + 3d**	**Wk 28**	**Wk 32**	**Wk 36**	**WK 40**	**Wk 44**	**Wk 48**	**Wk 48 + 3d**	**Wk 52**	**Wk 52 + 3d**
Written Informed Consent	X																			
Subject Demography	X																			
Medical History	X																			
SLE History	X																			
Therapy History	X																			
Eligibility Criteria	X																			
Biopsy Report[A]	X																			
Clinical Assessments																				
SELENA SLEDAI, SLE Flare Index and PGA		x					x			x				x					x	
SLICC Damage		x								x									x	
C-SSRS Screening/Baseline	X																			
C-SSRS Since Last Visit[B]		x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Record Concurrent Medications	X	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Complete Physical Exam	X																			
Symptom-driven Physical Exam		x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Weight[C]		x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Record/Assess Adverse Events		x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Laboratory Assessments																				
Hematology and chemistry (non-fasting)[D]	X	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Serum Creatinine[E]			x								x							x		x
Urinalysis[F]	X	x			x	x	x	x	x	x		x	x	x	x	x	x		x	
Urinary Microscopy[F]	X	x			x	x	x	x	x	x		x	x	x	x	x	x		x	
Spot urine	X	x			x	x	x	x	x	x		x	x	x	x	x	x		x	
24-hour Urine[E]		x								x							x		x	
BLyS protein (baseline only)		x																		
Pregnancy Test[G]	X	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
ANA	X	x								x									x	
Complement (C3/C4), anti-dsDNA	x	x			x	x	x	x	x	x		x	x	x	x	x	x		x	
acL (IgA, IgG, IgM isotypes)		x								x									x	

	Screening	Baseline	Double-Blind Treatment Period																	
Study Day	**-28 days**	**0**		**14±3 days**	**28±3 days**	**56±7 days**	**84± 7 days**	**112±7 days**	**140± 7 days**	**168± 7 days**		**196± 7 days**	**224± 7days**	**252± 7days**	**280± 7days**	**308± 7days**	**336± 7days**		**364± 7days**	
Study Week	**Wk -4**	**Wk 0**	**Wk 0 + 3d**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**WK 20**	**Wk 24**	**Wk 24 + 3d**	**Wk 28**	**Wk 32**	**Wk 36**	**WK 40**	**Wk 44**	**Wk 48**	**Wk 48 + 3d**	**Wk 52**	**Wk 52 + 3d**
Anti-Sm, antiC1q[H]		x								x									x	
Serum IgG	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Serum IgA & IgM	x	x				x				x									x	
PT/PTT	x	x				x				x									x	
HIV, HBsAg and hepatitis C antibody	x																			
Pharmacokinetic Sampling[I]		x	x	x	x	x				x	x								x	
Immunogenicity (anti-belimumab antibody)		x				x				x									x	
Peripheral B lymphocytes		x				x				x									x	
Pharmacogenetics Sampling (consenting subjects only)[J]		x																		
Study Agent Administration		x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	

[A]Biopsy report indicating proliferative lupus nephritis. Should be from a renal biopsy obtained in the 6 months prior to baseline (Day 0). Whenever possible, a tissue sample from the renal biopsy used to qualify the subject will be collected and sent to a central reading center; however, the tissue sample will not be shipped prior to nor be used for the purposes of randomization

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

[C]If weight changes by more than 5% from baseline (Day 0) weight, the weight at the current visit should be used for calculating the dose.

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

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

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

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

[H]Samples will be collected in all subjects at baseline (Day 0). Thereafter, samples will only be collected in subjects with positive results at baseline.

[I]For PK sampling times, see Section 6.10.1.

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

Table 6-2 Study Calendar - Double-Blind Treatment Period (Week 56-104)

	Double-Blind Treatment Period																	
Study Day	**392± 7days**	**420± 7days**	**448± 7days**	**476± 7days**	**504± 7days**	**532± 7days**		**560± 7days**	**588± 7days**	**616± 7days**	**644± 7days**	**672± 7days**	**700± 7days**		**Day 728/ Exit (4 weeks after last dose)[A]**		**8 week follow-up visit +7 days[B]**	**Unscheduled Visit[C]**
Study Week	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 76 + 3 d**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 100 + 3 d**	**Wk 104**	**Wk 104 + 3 d**		
Clinical Assessments																		
SELENA SLEDAI, SLE Flare Index and PGA			x			x				x					x			x
SLICC Damage						x									x			
C-SSRS Since Last Visit	x	x	x	x	x	x		x	x	x	x	x	x		x			
Record Concurrent Medications	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Symptom-driven Physical Examination	x	x	x	x	x	x		x	x	x	x	x	x		x			
Weight[C]	x	x	x	x	x	x		x	x	x	x	x	x		x			
Record/Assess Adverse Events	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Laboratory Assessments																		
Hematology and chemistry (non-fasting)[D]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	
Serum Creatinine[E]							x							x		x		
Urinalysis[F]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	
Urinary Microscopy[F]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	
Spot urine	x	x	x	x	x	x		x	x	x	x	x	x		x		x	
24-hour Urine[E]						x							x		x			
Pregnancy Test[G]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	
Complement (C3/C4), anti-dsDNA	x	x	x	x	x	x		x	x	x	x	x	x		x			
ANA, acL (IgA, IgG, IgM isotypes)						x									x			
Anti-Sm, antiC1q[H]						x									x			
Serum IgG			x			x				x			x		x			
Serum IgA & IgM						x									x			
PT/PTT						x									x			
Pharmacokinetic Sampling[I]															x		x	
Immunogenicity (anti-belimumab antibody)						x									x		x	
Peripheral B lymphocytes						x									x			
Study Agent Administration	x	x	x	x	x	x		x	x	x	x	x	x		**If entering extension**			

[A]For subjects completing all 100 weeks of treatment and continuing into the 6-month open-label extension, the Week 104 visit will also serve as Day 0 visit of the 6-month open-label extension. For subjects discontinued from the double-blind study early or subjects who are not continuing into the open label extension, the Week 104/Exit visit will occur approximately 4 weeks after the last dose of study agent. Only subjects who wish to continue in the open-label extension study will have study agent administered at the Week 104 visit after the completion of Week 104 assessments.

[B]The 8-week follow-up visit is to occur approximately 8 weeks after last dose of study agent for subjects withdrawing early and those subjects who do not continue into the 6-month open-label extension

[C]If weight changes by more than 5% from their Baseline (Day 0) weight, the weight at the current visit should be used for calculating the dose.

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

[E]Two 24 hour urine and serum creatinine collections will be performed for each of the following visits: Weeks 76, 100 and 104. The serum creatinine for these visits will be collected on the day of the initial visit and then 3 days after the initial visit. For the urinary sediment assessments, both menstrual cycles and genitourinary tract infections may be confounders. The urine collection may be postponed up to 14 days at the investigators discretion if menstrual bleeding or a genitourinary tract infection is present at anytime during the 24 hour urine collection.

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

[G]For women of child-bearing potential, a urine pregnancy test is required. The results of the urine pregnancy test must be available prior to dosing.

[H]Samples will only be collected in subjects with positive results at baseline.

[I]For PK sampling times, see Section 6.10.1.

6.4 Open-Label Extension

Subjects who successfully complete the initial 104-week double blind period and complete the Week 104 assessments may enter into a 6-month open-label extension. The Week 104 visit of the double-blind period will serve as the Day 0 visit for subjects entering the 6-month open-label extension. In the open-label extension, all subjects will receive 10 mg/kg belimumab every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the last dose). The first dose on the open-label extension will be given at the Week 104 visit of the double-blind period after the completion of Week 104 assessments. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety as per the study calendar (see Table 6-3).

During the open-label extension, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate. Prohibited medications and prohibited doses of medications as outlined in Sections 5.5 and 5.6 will still apply.

All subjects who withdraw early from the open-label extension will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent.

6.5 Continuation Phase – For Subjects in Countries where Belimumab is not Commercially Available

Subjects who complete dosing in the 6-month open-label extension and wish to continue treatment may do so by being prescribed commercially available product.

If belimumab is not commercially available in a subject's country of participation, subjects may continue to receive belimumab under this protocol until belimumab becomes commercially available. The Day 168/Week 24 visit from the 6-month open-label extension will serve as the Day 0 visit for subjects entering the continuation phase. Subjects will continue to receive belimumab every 28 days until belimumab becomes commercially available. The schedule of assessments representing a 48 week treatment period is provided in Table 6-4.

During the continuation phase, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate. Prohibited medications as outlined in Section 5.6 will still apply.

Table 6-3 Study Calendar- 6-Month Open-Label Extension

	Open Label Extension								
Study Day	**Day 0[A]**	**Day 28±3 days**	**Day 56±7 days**	**Day 84± 7 days**	**Day 112±7 days**	**Day 140± 7 days**	**Day 168± 7 days**	**Day 196± 7days/Exit [B] (4 weeks after last dose)**	**8 week follow-up visit +7 days[C]**
Study Week		**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**WK 20**	**Wk 24**	**Wk 28**	
Clinical Assessments	See Week 104 Visit in Double-Blind Treatment Period								
SELENA SLEDAI, SLE Flare Index and PGA								x	
SLICC Damage								x	
Record Concurrent Medications		x	x	x	x	x	x	x	x
Symptom-driven Physical Examination								x	
Weight		x	x	x	x	x	x	x	
Record/Assess Adverse Events		x	x	x	x	x	x	x	x
Laboratory Assessments									
Hematology and chemistry (non-fasting)[D]				x			x	x	x
Urinalysis[E]				x			x	x	x
Urinary Microscopy[E]				x			x	x	x
Spot Urine				x			x	x	x
Pregnancy Test[F]		x	x	x	x	x	x	x	x
C3/C4, anti-dsDNA							x	x	
Autoantibodies (acL, anti-Sm, ANA, antiC1q)							x	x	
Serum IgG			x				x	x	
Serum IgA & IgM							x	x	
Pharmacokinetic sampling[G]									x
Immunogenicity (anti-belimumab antibody)							x		x
Peripheral B lymphocytes							x	x	
Study Agent Administration	x	x	x	x	x	x	x	**If entering continuation**	

[A] Day 0 of the extension portion of the trial is the Week 104 study visit of the double-blind treatment period, and represents the first belimumab administration for those subjects continuing on the 6 month open-label extension.

[B] For subjects who discontinue from the study, an Exit visit should be completed 4 weeks after the last dose of study agent.

[C] The 8-week follow-up visit is to occur approximately 8 weeks after last dose of study agent for subjects withdrawing early from the open-label extension and for subjects who complete the open label extenstion and will not receive commercially available belimumab (in countries where available) or will not receive belimumab in the continuation phase (in countries where belimumab is not commercially available).

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

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

[F] For women of child-bearing potential, a urine pregnancy test is required. The results of the urine pregnancy test must be available prior to dosing

[G] For PK sampling times, see Section 6.10.1.

Table 6-4 Study Calendar- Continuation Phase (For Subjects in Countries where Belimumab is not Commercially Available)

Study Day	**Day 0[A]**	**Day 28 visit ± 3 days**	**Day 56 visit ± 7 days**	**Day 84 visit ± 7 days**	**Day 112 visit ± 7 days**	**Day 140 visit ± 7 days**	**Day 168 visit ± 7 days**	**Day 196 visit ± 7 days**	**Day 224 visit ± 7 days**	**Day 252 visit ± 7 days**	**Day 280 visit ± 7 days**	**Day 308 visit ± 7 days**	**Day 336 visit ± 7 days[E]**	**Exit[B]**	**8-week Follow-up ± + 7 Days[C]**
Study Week	See Week 28 Visit in Open-Label Extension	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**		
Record Concurrent Medications		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Record/Assess Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy Test[D]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Immunogenicity (anti-belimumab antibody)							x						x		x
Study Agent Administration	x	x	x	x	x	x	x	x	x	x	x	x	x		

[A]Day 0 of the extension portion of the trial is the Week 28 visit of the open-label extension, and represents the first belimumab administration for those subjects participating in the continuation phase.
[B]Any visit in which the subject discontinues treatment will become the Exit visit. Study agent should not be administered, and all Exit assessments must be completed.
[C] The 8-week follow-up visit is to occur approximately 8 weeks after last dose of study agent for subjects who withdraw from the continuation phase and will not be receive commercially available belimumab.
[D]For women of child-bearing potential, a urine pregnancy test is required. The results of the urine pregnancy test must be available prior to dosing

This calendar represents a yearly (48 week) ongoing visit schedule until the subject terminates the study. Week 4 of this calendar represents the next visit (after Week 28 from the 6-month open-label extension) for subjects continuing in this protocol where belimumab is not commercially available. Following completion of the Week 48 visit, for subjects in countries where belimumab is still not commercially available and wish to continue treatment, the study calendar will be repeated for subsequent years starting with the Week 4 visit.

6.6 Exit Visit

Subjects who drop out and do not complete the study must return for an Exit visit 4 weeks after the final dose of study agent.

During the double-blind treatment period, the assessments for the Week 104 visit will be performed for the Exit visit. During the open-label extension, the assessments for the Week 28 visit will be performed for the Exit visit.

Refer to the Study Calendar (Table 6-2 and Table 6-3) for a list of procedures required at this visit.

6.7 8-Week Follow-up Visit

All subjects must return for a follow-up visit approximately 8 weeks after the last dose of study agent.

Refer to the Study Calendar (see Table 6-2, Table 6-3 and Table 6-4) for a list of procedures required at this visit.

6.8 Unscheduled Visits

Unscheduled visits may be necessary during the course of the study to capture a subject's status between regularly scheduled visits. Examples include, but are not limited to, a worsening of lupus nephritis symptoms, AE reporting, or follow-up to a previously reported AE.

Whenever possible, a complete disease activity assessment (SELENA SLEDAI, SLE Flare Index and PGA), and laboratory assessments (hematology, chemistry, urinalysis, anti-dsDNA, and complement) should be performed to document disease activity worsening (eg, renal flare/relapse) prior to instituting treatment that results in treatment failure designation as defined in Sections 5.5 and 5.6.

Refer to the Study Calendar (Table 6-2 and Table 6-3) for a list of procedures required at these visits. Other assessments should be performed as clinically indicated.

6.9 Renal Biopsies

Whenever possible, a tissue sample from the renal biopsy used to qualify the subject will be collected and sent to a central reading center; however, the tissue sample will not be shipped prior to nor be used for the purposes of randomization. Tissue from any renal biopsies performed as part of routine care anytime after baseline (Day 0) will also be collected, where possible, for a similar central reading.

6.10 Laboratory Tests

Non-fasting clinical laboratory tests will be performed as outlined in the Study Calendar (see Table 6-1, Table 6-2, and Table 6-3).

Due to the potential for unblinding, the following lab results will not be provided to study sites after baseline (Day 0): aCL (IgM, IgG, IgA isotypes), ANA, anti-Sm, anti-C1q, and serum immunoglobulin isotypes IgM/IgA.

In geographies where feasible, the following biological markers will be measured (using FACS analysis):

- Peripheral B lymphocytes:
  $CD20^+$, $CD20^+/27^+$ memory, $CD20^+/27^-$ naïve, $CD20^+/69^+$ activated, $CD20^+/138^+$ plasmacytoid, $CD19^+/27^{BRIGHT}/38^{BRIGHT}$ SLE subset, $CD19^+/CD24^{HIGH}/CD38^{HIGH}$ regulatory B cell and $CD20^-/138^+$ plasma cells.

For the renal function assessments at Baseline (Day 0), Week 24, 48, 52, 76, 100 and 104, the glomerular filtration rate (GFR) will be based on creatinine clearance determined from the mean creatinine value of 2 contiguous 24 hour urine collections and 2 serum creatinine measurements (first serum creatinine collected at initial visit and the second sample taken 3 days later at the follow-up visit). Subjects will be provided with the materials for collecting the two 24 hour urine collections beginning the next morning following their initial clinic visit. On the third day following the initial visit, subjects will return to the clinic for the second serum creatinine sample. For all other study visits, the simplified MDRD formula (below) will be used to estimate GFR (Levey et al, 2000):

$$eGFR = 186 \times \text{serum creatinine}^{-1.154} \times Age^{-0.203} \times [1.212 \text{ if Black}] \times [0.742 \text{ if Female}]$$

The serum creatinine concentration is expressed in mg/dL.

It has been demonstrated that there is a strong correlation between the protein content of a 24-hour urine collection and the urinary protein: urinary creatinine ratio in a single urine sample (Ginsberg et al, 1983; Ruggenenti et al, 1998; KDOQI Clinical Practice Guidelines for Chronic Kidney Disease 2002; Price et al, 2005). Given this information, spot urinary protein: urinary creatinine ratio will be used for determining proteinuria in this study for renal response assessments and the SELENA SLEDAI (Appendix 3) disease activity indices when a 24-hour urine sample is not collected.

For the urinary sediment assessments, both menstrual cycles and genitourinary tract infections may be confounders. The urine collection may be postponed up to 14 days at the investigators discretion if menstrual bleeding or a genitourinary tract infection is present at anytime during the 24 hour urine collection.

Additional instructions regarding collection procedures are provided in the Study Procedures Manual and Central Laboratory Manual.

6.10.1 Pharmacokinetics

All randomized subjects will be sampled for serum belimumab levels. A blood sample for pharmacokinetic analysis will be drawn according to the time schedule below.

Table 6-5 PK Visit Days and Sample Times

Day (Week)	Time (Related to Dosing of Study Agent)
Day 0	Before the start of infusion
Day 3	Anytime during visit
Day 14 (Week 2)	Prior to dosing, 0-4 hours after the end of infusion
Day 28 (Week 4)	Prior to dosing, 0-4 hours after the end of infusion
Day 56 (Week 8)	Prior to dosing
Day 168 (Week 24)	Prior to dosing, 0 - 4 hours after the end of infusion
Day 171 (Week 24 + 3 days)	Anytime during visit
Day 364 (Week 52)	Prior to dosing
Day 728/Exit (Week 104)	Anytime during visit (or prior to dosing if going into the open-label treatment period of the study)
8-week follow-up	Any time during visit

On days study agent is administered and blood samples for pharmacokinetic analysis are obtained after infusion, blood samples for pharmacokinetic analysis should not be taken from the same arm as that used for the administration of study agent. Samples may be obtained by venipuncture.

Detailed instructions regarding the collection, processing, storage and shipment of blood samples are available in the Study Procedures Manual that is provided to all study sites**.**

6.10.2 Immunogenicity

Serum samples for anti-belimumab antibody measurements will be obtained from all randomized subjects before administration of study agent at baseline (Day 0), and at any time on Week 8, Week 24, Week 52, Week 76 and Week 104 in the double-blind portion of the study. During the open-label extension, a sample will be collected at Week 24. Additionally, a sample will be collected at the 8-week follow-up visit. For any subject who had a positive antibody response at the 8-week follow-up visit (or last study visit at which immunogenicity was assessed if 8-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or after completion and/or unblinding of the study, whichever is later.

6.11 Withdrawal of Subjects from Treatment

In addition to the reasons for withdrawal detailed below, subjects are free to withdraw from treatment or from the study at any time, for any reason, or may be withdrawn/removed, if necessary, to protect their health. It is understood by all concerned that an excessive rate of

withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided. Subjects who withdraw from treatment/ study after receiving at least 1 dose of study agent will not be replaced.

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

- Prohibited concurrent medication or prohibited dose of concurrent medication (see Sections 5.5 and 5.6).
- Prohibited therapy.
- Unacceptable toxicity (see Section 5.4).
- Pregnancy.
- Withdrawal of consent (including use and disclosure of research-related health information).

All subjects who discontinue treatment during the double-blind period (for reasons other than receipt of prohibited medications or doses of medication that result in treatment failure designation or withdrawal of consent) should return for all scheduled visits through Week 104.

All subjects who discontinue treatment during the double-blind period for receipt of prohibited medications or doses of medication that result in treatment failure designation, or discontinue treatment during the open-label extension or continuation phase must complete the Exit visit (4 weeks after the last dose of study agent) and a follow up visit 8 weeks after the last dose of study agent.

In the event that a subject withdraws consent during the double-blind period, an attempt should be made at the time of consent withdrawal to obtain consent to obtain survival status at Week 104. Any subject that withdraws consent for use and disclosure of research-related health information will be considered withdrawn from the study and not followed for mortality.

6.12 Subject Unblinding

Belimumab and placebo will be supplied as open-label vials and 3rd party unblinding will be employed. The study agent will be reconstituted and diluted by the unblinded site pharmacist or designee, independent of the study (person responsible for receiving and dispensing study agent). Except for a limited number of safety oversight personnel, all study site personnel, the subject, the sponsor and the Contract Research Organization (CRO) remain blinded to the study agent received and to the results of certain biomarker and pharmacodynamic laboratory results. Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

If a medical emergency occurs and a decision regarding the subject's condition requires knowledge of the treatment assignment, the study blind may be broken for the specific subject. Unless the medical emergency is deemed to be life-threatening, the Medical Monitor

must be consulted prior to unblinding. Any broken blind will be clearly justified and explained by a comment in the eCRF. The investigator must notify the Medical Monitor of any broken blind, regardless of whether it was done for emergency or non-emergency reasons.

7 Adverse Event Reporting

7.1 Definitions

ADVERSE EVENT (EXPERIENCE): Any unfavorable or unintended sign, symptom, or disease that is temporally associated with the use of a study agent but is not necessarily caused by the study agent. This includes worsening (eg, increase in frequency or severity) of preexisting conditions.

SERIOUS ADVERSE EVENT: An adverse event resulting in any of the following outcomes:

- death
- is life-threatening (ie, an **immediate** threat to life)
- inpatient hospitalization*****
- prolongation of an existing hospitalization
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- is medically important[+]

*****An inpatient hospitalization is defined as an admission for any length of time. A hospitalization for administration of study agent, for routine or planned clinical procedures, or for "social" reasons (not the result of any adverse change in the subject's condition) should not be considered an adverse event and should not be reported as a serious adverse event. If the subject experiences any adverse change in condition during hospitalization, the condition must be reported as an adverse event or serious adverse event according to the above definitions.

[+]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. (ICH guidelines, March 1995)

UNEXPECTED ADVERSE EVENT: An adverse event, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved study agent or package insert/summary of product characteristics for an approved product). Expected means the event has previously been observed with the study agent and is identified and/or described in the applicable product information. It does not mean that the event is expected with the underlying disease(s) or concomitant medications.

7.2 Reporting Adverse Events to the Sponsor

All adverse events (AEs) that are identified from the start of study agent administration (Day 0) through 8 weeks following administration of the last dose of study agent will be recorded on the Adverse Event Case Report Form (AE eCRF). All data fields on the AE eCRF must be completed.

Serious Adverse Events (SAEs) must ALSO be recorded on the SAE Worksheet and sent to the Drug Safety designee within 24 hours of site personnel becoming aware of the SAE, regardless of expectedness. All pages of the SAE Worksheet should be completed, but the SAE Worksheet should not be held until all information is available. Additional information and corrections should be provided on subsequent SAE Worksheets as described in the Study Procedures Manual. SAE Worksheets should be sent either via the EDC system, if SAE EDC functionality is available or by facsimile to the HGS Drug Safety designee using the fax number listed on the SAE Worksheet.

7.3 Other Events Requiring Rapid Reporting (Protocol Specified Events)

Protocol Specified Events (PSEs) are additional events that must be reported to the Drug Safety designee in an expedited manner. A PSE may or may not be an SAE. PSEs are considered SAEs if they meet 1 or more of the criteria for an SAE (See Section 7.1). PSEs are recorded on SAE Worksheets and sent to the Drug Safety designee within 24 hours of site personnel becoming aware of the event.

IgG < 250 mg/dL (Grade 4) is a protocol specified event for this protocol.

7.4 Laboratory Abnormalities as Adverse Events

A laboratory abnormality should be reported as an adverse event if it is associated with an intervention. Intervention includes, but is not limited to, discontinuation of treatment, dose reduction/delay, or concomitant therapy. In addition, any medically important laboratory abnormality may be reported as an adverse event at the discretion of the investigator. This includes laboratory abnormalities for which there is no intervention but the abnormal value(s) suggests a disease or organ toxicity. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine RBC increased). In addition, an IgG abnormality < 250 mg/dL (Grade 4) should be recorded as an adverse event (and SAE if meeting the criteria in Section 7.1).

Laboratory tests are graded according to the Adverse Event Severity Grading Tables in Appendix 7. If a particular lab test is not listed in the Appendix, the lab test should be graded mild, moderate, severe or life-threatening as specified in Section 7.8.

7.5 Progressive Multifocal Leukoencephalopathy

There have been no reported cases of PML in subjects with SLE or RA treated with belimumab. However, patients with SLE may be at increased risk for PML secondary to SLE

itself, as well as the concurrent use of immunosuppressive drugs. The most common signs and symptoms of PML include visual disturbances, ocular movements, ataxia, and mental status changes such as disorientation or confusion. Clinical signs and symptoms of PML and SLE can be similar. The investigator must exercise best judgment in further workup and clinical intervention as appropriate. If PML is suspected, this should be promptly reported to the sponsor.

7.6 Suicidality Assessment

Some autoimmune diseases have an increased risk of suicidal behaviour and/or ideation (Bachen, 2009; Timonen, 2003; Stenager, 1992). In order to objectively assess suicidality in belimumab clinical programs the C-SSRS (Appendix 8 and Appendix 9) will be utilized to collect information on suicidal behavior and ideation. SLE patients have an increased prevalence of mood and anxiety disorders compared with the general population and disease activity may contribute to this higher risk. The incidence of major depressive disorder (MDD) among SLE patients has been reported to be as high as 47% (Bachen, 2009). Since active SLE and MDD may increase the risk of suicidal ideation or behavior before or during clinical studies, subjects participating in the double-blind portion of this study will be assessed for suicidality at every visit.

Subjects who answer “yes” to any suicidal behavior or “yes” to suicidal ideation questions 4 or 5 on the C-SSRS should be referred to appropriate psychiatric care and prompts the completion of an SAE worksheet. The medical monitor should be notified when these events occur. In addition, a “yes” to any suicidal behavior or “yes” to suicidal ideation question 3, 4 or 5 on the C-SSRS prompts the completion of the Possible Suicidality Related History Questionnaire (PSRHQ, only the first time this condition is met) eCRF and a Possible Suicidality Related Questionnaire (PSRQ) eCRF (at all times this condition is met).

Baseline/Screening and during treatment assessment of suicidality will be performed during the blinded portion of this study using C-SSRS (Refer to Appendix 8 and Appendix 9 for C-SSRS). The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both behaviour and ideation (Posner, 2007). The C-SSRS is administered by a qualified clinician and is designed to address the need for a summary measure to track change in the severity/density of suicidality across both clinical settings and treatment trials. It assesses intensity of ideation (a potentially important marker of severity) by specifically asking about frequency, duration, intrusiveness, controllability, and deterrents. In addition, it captures both the modal and most severe forms of ideation. The C-SSRS is to be completed by the investigator or his/her qualified designee at every visit during the double-blind portion of the study.

Although assessment of suicidality using the C-SSRS will take place only during the blinded portion of the study, investigators are reminded of the importance to clinically assess for suicidality at every visit given that SLE patients are at increased risk of suicidal behavior and/or ideation.

7.6.1 Possible Suicidality Related Questionnaire (PSRQ)

The investigator will be prompted to complete the PSRQ (in addition to the AE, SAE pages, and PSRHQ as appropriate) if a "yes" response is given to any suicidal behaviour or a "yes" response to suicidal ideation questions 3, 4 or 5 on the C-SSRS. If the adverse event meets the definition of an SAE, which includes a "yes" answer to any suicidal behaviour or a "yes" to suicidal ideation questions 4 or 5 on the C-SSRS, the site must ensure that there are no significant discrepancies between the PSRQ and SAE.

7.7 Reporting a Pregnancy

Pregnancies must be reported to the Drug Safety designee within 24 hours of the site becoming aware of a pregnancy in a subject. All pregnancies that are identified from the start of study agent through 16 weeks following the last dose of study agent should be reported. All pregnancies are tracked up to term or delivery following the last study agent treatment. When pregnancy is reported, HGS Drug Safety sends an acknowledgement memorandum to the principal investigator along with a Pregnancy Assessment Form. A Pregnancy Assessment Form must be completed every three months until live birth, elective termination of the pregnancy, or miscarriage. The site is responsible for following the subject's pregnancy to final outcome.

Pregnancies are not considered adverse events. Complications or medical problems associated with a pregnancy are considered AEs and may be SAEs. Complications or medical problems are reported as AEs/SAEs according to the procedure described in Section 7.2

7.8 Investigator Evaluation of Adverse Events

The investigator will evaluate all adverse events with respect to seriousness, severity (intensity or grade), and causality (relationship to study agent). The criteria for serious are listed in Section 7.1. The severity of an AE is to be evaluated according to the Adverse Event Severity Grading Tables in Appendix 7. If an AE does not have Adverse Event Severity Grading in Appendix 7, the following severity classifications will be used:

SEVERITY:

- **Grade 1- Mild** - causing no limitation of usual activities.
- **Grade 2- Moderate** - causing some limitation of usual activities.
- **Grade 3- Severe** - causing inability to carry out usual activities.
- **Grade 4- Life-threatening*** - potentially life-threatening or disabling; significant medical intervention is required.

*Note – a severity assessment of Life-threatening is not necessarily the same as the seriousness criterion of Life-threatening. (See "Serious" Criteria Section 7.1.) The former means that the event is a potential threat to life. The latter means that the event is an immediate threat to life.

CAUSALITY:

Definitely Related	- reasonable temporal relationship to study agent administration - follows a known response pattern (eg, study agent is known to cause this AE) - there is no alternative etiology
Probably Related	- reasonable temporal relationship - follows a suspected response pattern (eg, based on similar drugs) - no evidence for a more likely alternative etiology
Possibly Related	- reasonable temporal relationship - little evidence for a more likely alternative etiology
Probably Not Related	- does not have a reasonable temporal relationship OR - good evidence for a more likely alternative etiology
Not Related	- does not have a temporal relationship OR - definitely due to alternative etiology

The causality assessment must be made by the investigator based on information available at the time that the AE eCRF or SAE worksheet is completed. The initial causality assessment may be revised as new information becomes available.

7.9 Follow-up of Adverse Events

Adverse events that occur from the start of study agent administration through 8 weeks after the date of last administration of study agent are followed until final outcome is known or until the end of the 8-week study follow-up period. Adverse events that have not resolved at the end of the 8-week study follow-up visit are recorded on the adverse event case report form (AE eCRF) as ONGOING.

SAEs that have not resolved by the end of the follow-up period are followed until final outcome of recovered or recovered with sequelae is achieved. If it is not possible to obtain a final outcome for a particular SAE (eg, the subject is lost to follow-up), then the reason a final outcome could not be obtained must be documented by the investigator.

7.10 Post Study Serious Adverse Events

SAEs that occur after the follow-up period (ie, 8 weeks after the last dose of the study agent) that are assessed by the investigator as having as definitely, possibly or probably related to study agent must be reported to the Drug Safety designee on the SAE worksheet as described in Section 7.2. Post study SAEs will not be documented on the AE eCRF.

7.11 Reporting Serious Adverse Events to Regulatory Authorities and Institutional Review Boards/Independent Ethics Committees

All SAEs that are considered by the sponsor to be unexpected and related to belimumab will be reported by the sponsor or designee as expedited (ie, 15-Day) reports to the appropriate regulatory authorities AND to all participating investigators (exceptions discussed below). In addition, the sponsor or designee follows all applicable local and national regulatory requirements regarding safety reporting.

All unexpected SAEs that are reported to the Sponsor as related to the study agent will be reported to investigators and IRBs/IECs irrespective of whether, upon unblinding by the Sponsor, the subject is known to have received belimumab or placebo. This will insure that investigators and other investigational site staff do not become unblinded during the study. Each investigator must also comply with the applicable regulatory requirements related to the reporting of SAEs to the IRBs/IECs responsible for reviewing the study at their site, as well as the regulatory authority(ies) (if applicable). Regulatory authorities that receive such reports directly from the Sponsor will receive unblinded reports for those events where the subject was receiving belimumab.

All serious adverse events, including serious disease-related events (discussed below), will be monitored by treatment group by an independent DMC (Section 8.3). Investigators and IRBs/IECs will be notified of the outcome of each DMC meeting, and any recommendations made.

The following conditions (preferred terms; MedDRA v. 14.0) are disease related events that can occur in the study population regardless of belimumab exposure. When these conditions are considered SAEs, they must be reported to the sponsor within 24 hours of site personnel becoming aware as described in Section 7.2. The sponsor will not submit these events as expedited reports to regulatory authorities, participating investigators, or IRBs/IECs (unless considered by the sponsor to be related to study agent).

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

8 Endpoints and Statistical Analysis

8.1 General Statistical Considerations

Unless otherwise specified, all analyses will be performed on the ITT population defined as all subjects who are randomized and receive at least 1 dose of study agent. The ITT analysis will be performed according to the treatment that a subject was randomized to receive, regardless of the actual treatment received.

The database will be locked for primary analysis after data through the Week 104 visit for all subjects have been collected, verified and validated. All subjects and study site personnel will remain blinded until the final database lock, which will occur after data have been collected, verified and validated for all subjects completing the 8 week follow-up after the open-label extension.

For the analysis of the primary and the major secondary efficacy endpoints, a step-down sequential testing procedure will be used to control the overall type 1 error. With this procedure, the primary and 2 major secondary endpoints will be evaluated for statistical significance based on a pre-specified sequence for interpretation: (1) renal response (complete, partial or no response) at Week 104 (2) renal response (complete, partial or no response) at Week 52, and (3) complete renal response at Week 104. 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, although nominal p values may be reported and considered descriptive.

Analyses of other efficacy endpoints other than the major secondary efficacy endpoints will not be subject to any multiple testing procedure. All statistical tests will be 2-sided and performed at an overall significance level of 0.05.

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

8.2 Randomization Procedure and Assignment to Treatment Groups

This is a Phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled study. Once subjects have consented, have undergone all screening procedures and have been determined to be eligible for the study, they will return for the baseline (Day 0) visit to be randomized in a 1:1 ratio (via an Interactive Web Response System) to 1 of 2 treatment groups (10 mg/kg belimumab plus standard of care or placebo control plus standard of care. The randomization of all eligible subjects will be stratified by their induction regimen (HDCS plus CYC vs HDCS plus MMF) and race (black race vs other).

8.3 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will review unblinded safety data for this Phase 3 program on an ongoing basis until the data are locked and analyzed through Week 104 (after which monitoring may be assumed by an internal HGS committee). The DMC will include at least 3 physicians and a statistician, none of whom are affiliated with the sponsor. The DMC will review the data approximately every 4 months. At all times the sites and sponsor will remain blinded to treatment allocation. Events to be monitored during the safety review will include, at a minimum, all serious adverse events (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 and open-label extension portions of the study. Investigators and IRBs/IECs will be notified of the outcome of each DMC meeting.

The DMC will receive information within 72 hours of the sponsor or designee receiving notification of any IgG < 250 mg/dL and all unexpected causally-related SAEs that are life threatening or result in death. Other unexpected, causally-related SAEs will be provided to the DMC within 15 calendar days. In addition, the DMC will receive information on all serious infections and all opportunistic infections, irrespective of relationship to study agent, within 15 calendar days.

8.4 Sample Size Rationale

It is expected that approximately 50% subjects on placebo plus standard of care will have complete (10%) or partial renal response (40%) at the Week 104 visit (Appel et al, 2009; Sinclair et al, 2007). It is expected that renal response in subjects on belimumab plus standard of care will be approximately 65% (Complete=15%, Partial=50%). Approximately 464 subjects will be randomized to achieve 232 subjects in each treatment arm providing approximately 90% power to detect the difference in the primary endpoint, based on a 2-sided Van Elteren test at the 5% significance level (Zhao et al, 2008).

8.5 Efficacy

8.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is renal response at Week 104 measured as an ordinal response - complete renal response, partial renal response, or no renal response. Renal response is determined by changes in urinary sediment, proteinuria, and renal function. Week 104 renal response will be defined by a response at the Week 100 visit that is confirmed by a repeat measurement at the Week 104 visit. Renal response is defined as follows:

- Complete Renal Response:

  Calculated glomerular filtration rate (GFR) is within normal range

  AND

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

AND

Urinary protein:creatinine ratio < 0.5

(Note: For subjects with a normal urinary sediment and GFR at baseline and only the presence of proteinuria (≥ 3.5 grams/day), the urine protein:creatinine ratio should be < 0.5 to meet the primary endpoint)

- Partial Renal Response:

  Estimated or calculated GFR no more than 10% below the baseline value or within normal range

  AND

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

  AND

  ≥ 50% decrease in the urine protein:creatinine ratio with one of the following:
  - a urine protein:creatinine ratio of < 1.0, if the baseline ratio was ≤ 3.0
    OR
  - a urine protein:creatinine ratio of < 3.0, if the baseline ratio was > 3.0

- No Renal Response:

  Not meeting criteria for either complete or partial renal response

The renal response at the Week 104 visit will be derived as below:

Week 100 Renal Response	Week 104 renal Response	Final Week 104 Renal Response
Complete	Complete	Complete
Complete	Partial	Partial
Partial	Complete	Partial
Partial	Partial	Partial
Complete	No Response	No Response
Partial	No Response	No Response
No response	Complete	No Response
No response	Partial	No Response

Renal response at the Week 52 visit will be derived using a similar approach to that described above for the Week 104 visit, but using the Week 48 and Week 52 visits.

For a complete response to be declared at Week 104, a calculated GFR (using sequential 24 hour urine collections as defined in Section 6.10) should be available for both of the Week 100 and 104 assessments. However, if a calculated GFR is only available for one of the timepoints, a complete response can be based on estimated GFR (MDRD, as defined in Section 6.10) for the missing calculated GFR assessment. If calculated GFR is missing for both assessments, then the best response possible will be partial response using estimated GFR. The same approach will be taken at Week 52.

At all other timepoints, complete and partial responses can be based on calculated or estimated GFRs.

8.5.2 Primary Efficacy Analysis

Renal response (complete, partial, or no renal response) at the Week 104 visit will be compared between the belimumab plus standard of care treatment group and placebo plus standard of care using the Van Elteren test, stratified by baseline randomization factors.

Any subject who receives a protocol-prohibited medication or dose will be considered a treatment failure (ie, non-responder) for the primary endpoint. Subjects who do not receive protocol-prohibited medication/dose, but discontinue study agent should remain on study and undergo protocol required assessments through Week 104. Subjects who are not treatment failures but are withdrawn from the study prior to the Week 104 visit will have the primary endpoint imputed as follows:

- No Response:
  - If withdrawn before Week 52.
  - If withdrawn after Week 52, but had a response that was maintained < 24 weeks at the time of last contact.
  - If no response at the time of last contact.

- Partial Response:
  - If withdrawn after the Week 52 visit and had a response that had been maintained for $\geq$ 24 weeks at the time of last contact the patient will be considered to have a partial renal response. Complete renal response will not be imputed.

8.5.2.1 Missing Values

The following imputation method will be used to handle a missing visit related to the primary endpoint assessment:

- If the Week 104 visit is missing, the primary endpoint will be determined using data from the Week 96 and the Week 100 visits.

- If the Week 100 visit is missing, the primary endpoint will be determined using data from the Week 96 and the Week 104 visits.
- If a subject misses both the Week 100 and the Week 104 visit, the subject's response will be imputed as follows. If the subject had a response at or after the Week 52 visit that was maintained for $\geq$ 24 weeks at the time of last contact, the subject will be considered to have a partial renal response. Otherwise, the subject will be defined as a non-responder.

If 2 or more components of the primary endpoint for a subject are missing at a visit (Week 100 or Week 104), all 3 components at this visit will be considered missing unless the subject has been determined as a non-responder based on the available data. If only 1 component of the primary endpoint is missing at only 1 visit, the following imputation method will be used for subjects missing a component of the primary endpoint:

- If this component is missing at the Week 104 visit, the missing component will be determined using data on the component from the Week 96 and the Week 100 visits.
- If this component is missing at the Week 100 visit, the missing component will be determined using data on the component from the Week 96 and the Week 104 visits.
- If this component is missing at both the Week 100 and the Week 104 the subject's response will be imputed as follows. If the subject had a response on the missing component at or after the Week 52 visit that was maintained for $\geq$ 24 weeks at the last contact, the subject will be considered to have a partial response on the missing component. Otherwise, the subject will be defined as a non-responder.

The parallel approach will be taken at Week 52.

8.5.2.2 Sensitivity Analyses

The robustness of the primary efficacy results will be assessed by comparing renal response (complete, partial or no renal response) at the Week 104 visit between treatment groups in the completer population. The completer population is defined as all subjects who are on treatment through the Week 100. The analysis will be performed using the Van Elteren test, stratified by baseline randomization factors. Any subject who receives a protocol-prohibited medication or dose will result into a treatment failure in this analysis.

Other sensitivity analyses will be specified in the statistical analysis plan.

8.5.2.3 Subgroup Analysis

Subgroup analysis of the primary efficacy endpoint (ie, renal response at Week 104) will be performed in the following subgroups:

- Induction regimen (HDCS plus CYC vs HDCS plus MMF).
- Race (black vs other).
- Region (US/Canada, Europe/Australia/Israel, Asia, Americas excluding US and Canada).
- Baseline anti-dsDNA (anti-dsDNA $\geq$ 30 IU/mL vs other).

- Baseline complement (C3 and/or C4 low vs other).
- Baseline complement and anti-dsDNA (C3 and/or C4 low AND anti-dsDNA ≥ 30 IU/mL vs other).

8.5.3 Secondary Efficacy Endpoints

8.5.3.1 Major Secondary Efficacy Endpoints

- Renal response measured by complete, partial or no response at Week 52.
- Proportion of subjects who achieve complete renal response at Week 104.

8.5.4 Other Efficacy Endpoints

Disease activity

- Mean and median percentage change from baseline in SELENA SLEDAI score by visit.
- Proportion of subjects with a ≥ 4 point reduction in SELENA SLEDAI from baseline score by visit.
- Proportion of subjects with a ≥ 5 point reduction in SELENA SLEDAI from baseline score by visit.
- Proportion of subjects with a ≥ 6 point reduction in SELENA SLEDAI from baseline score by visit.
- Proportion of subjects with a ≥ 7 point reduction in SELENA SLEDAI from baseline score by visit.
- Proportion of subjects with improvement and worsening in SELENA SLEDAI organ systems (Bombardier, 1992) from baseline by visit.
- Mean and mean percent change from baseline in SELENA SLEDAI excluding renal items by visit.

Flares*

- Time to first renal flare and the rate of renal flare from Week 24 among subjects with PRR or CRR at Week 24.
- Time to first renal flareand the rate of renal flare from Week 52 among subjects with PRR or CRR at Week 52.
- Time to first severe flare.
- Time to severe flare after Week 24.
- Rate of severe flare per 100 subject years over 104 weeks.

*Renal flare will be defined according to FDA Guidance (June 2010); Severe flare will be defined by using the modified SLE Flare Index. Both definitions will be included in full in the statistical analysis plan.

Renal Specific Measures

- Individual components of renal response. Proportion of subjects with the following by visit:
  - Inactive urinary sediment (< 5 RBCs/hpf and < 5 WBCs/hpf or within the reference range of the laboratory); and no cellular casts (no RBC or WBC casts).
  - RBCs/hpf ≥ 50% reduction from baseline and no RBC casts.
  - Urinary protein:creatinine ratio < 0.5.
  - ≥ 50% improvement in the urine protein:creatinine ratio with one of the following: a urine protein:creatinine ratio of < 1.0, if the baseline ratio was ≤ 3.0 **OR** a urine protein:creatinine ratio of < 3.0, if the baseline ratio was > 3.0.
  - GFR within the normal range.
  - GFR no more than 10% below the baseline value.
- Percent change in proteinuria by visit.
- Proportion of subjects with a doubling of the serum creatinine or progression to end stage renal disease (ESRD) as defined below:
  - Doubling of serum creatinine compared with baseline that is confirmed with a second measurement at least 3 weeks later.
  - Progression to ESRD defined as the need for chronic dialysis or renal transplantation.
- Duration of longest complete or partial renal response (CRR/PRR) in all subjects achieving at least 1 response.
- Duration of CRR in all subjects achieving at least 1 CRR.
- Time to first PRR/CRR that is maintained through Week 52.
- Time to the first PRR/CRR that is maintained through Week 104.
- Time to the first CRR that is maintained through Week 52.
- Time to the first CRR that is maintained through Week 104.
- Time to sustained (≥ 3months) complete or partial renal response (CRR/PRR) after Week 24.
- Time to sustained (≥ 3months) CRR after Week 24.
- Proportion of subjects with CRR by visit.
- Proportion of subjects with CRR and/or PRR by visit.

Corticosteroid Use

- Proportion of subjects receiving ≤ 5 mg/day prednisone by visit.
- Proportion of subjects receiving ≤ 10 mg/day prednisone by visit.

Biomarkers

1. Median/mean percent change and median/mean absolute change from baseline in absolute B cell subsets ($CD20^+$, $CD20^+/27^+$ memory, $CD20^+/27^-$ naïve, $CD20^+/69^+$ activated, $CD20^+/138^+$ plasmacytoid, $CD19^+/27^{BRIGHT}/38^{BRIGHT}$ SLE subset,

$CD19^{+}/CD24^{HIGH}/CD38^{HIGH}$ regulatory B cell, and $CD20^{-}/138^{+}$ plasma cells) by visit. Only in regions/countries where assessment of B cells is feasible.

2. Median/mean percent change and median/mean absolute change from baseline by visit
   - Total serum immunoglobulin (IgG and other isotypes: IgM and IgA).
   - Autoantibodies* (anti-dsDNA, ANA, aCL, anti-Sm, and anti-C1q).
   - Complement (C3, C4) levels.
3. Percent of patients with normalized serological activity at Week 104 and over time
   - IgG, IgM and IgA (high to normal/low).
   - Autoantibodies* (anti-dsDNA, ANA, aCL, anti-Sm, and anti-C1q) present to absent.
   - Complement (C3, C4, and C3 AND C4) levels low to normal/high.

* Anti-dsDNA will be collected monthly throughout the double-blind treatment period. Other autoantibodies will be collected from all patients at baseline, then at regular intervals during the study.

8.5.5 Secondary Efficacy Analyses

8.5.5.1 Major Secondary Efficacy Analyses

Renal response (complete, partial or no response) at the Week 52 visit will be analyzed using the same method as for the primary endpoint. The proportion of subjects who achieve a complete renal response at the Week 104 visit will be compared between the belimumab treatment group and placebo using a logistic regression model. The independent variables in the model will include treatment group (ie, 10 mg/kg belimumab vs placebo) and the baseline randomization stratification factors.

8.5.6 Other Efficacy Analyses

The analysis of all other efficacy endpoints will be described in the statistical analysis plan.

8.6 Safety

8.6.1 Definition of Safety Variables

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

8.6.2 Analysis of Safety Variables

AEs will graded for severity by the investigator using Adverse Event Severity Grading Tables (Appendix 7) or the grades in Section 7.8, as appropriate. The frequency of AEs will be tabulated by MedDRA system organ class (SOC) and preferred term. Additional analysis may be performed based on event rates adjusting for subject-years on study agent if the dropout rates are unbalanced across treatment groups. AEs will also be summarized by MedDRA SOC and preferred terms for those that are considered to be severe (Grade 3 and Grade 4) and those that are considered serious. Discontinuations due to AEs will be summarized.

The frequency of laboratory abnormalities will be tabulated by treatment group. Laboratory values will be assessed for significant changes from baseline. Laboratory toxicity will be

graded using Adverse Event Severity Grading Tables (Appendix 7) when possible. Shift tables will be used to determine if subjects move from normal to abnormal during the course of the study. Shifts of ≥ 2 grades and Grade 3 or 4 laboratory abnormalities will be summarized.

Safety Endpoints of Special Interest

- All cause mortality
- Serious and/or severe infections
- Opportunistic infections
- Malignant neoplasms
- Selected serious psychiatric events
- Suicidality assessment (see Appendix 8 and Appendix 9)
- Hypersensitivity reactions/anaphylaxis
- Immunogenicity

The analyses of these safety endpoints will be described in the statistical analysis plan.

8.7 Pharmacokinetics

8.7.1 Definition of Pharmacokinetic Evaluation

All randomized subjects will be sampled for serum belimumab levels. Serum belimumab concentration data will be used in a population PK analysis. Assessment of belimumab concentrations will be performed at the timepoints indicated in Section 6.10.1.

8.7.2 Analysis of Pharmacokinetics

Serum belimumab concentration will be determined by an electrochemiluminescence (ECL)-based assay. Results for this study will be presented using appropriate graphic and tabular summaries. Serum belimumab concentration data obtained from this study will be used in a population PK analysis, which will be reported separately. Potential effects of demographic and disease characteristics, concurrent medications or renal function on belimumab PK will be evaluated.

9 Pharmacogenetics (PGx)

In consenting subjects, a blood sample for PGx research will be drawn predose at baseline (Day 0) to better characterize genetic variability (eg, HLA typing) that may affect efficacy or safety endpoints. Information regarding PGx research is included in Appendix 6.

The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the study site. The approval(s) must be in writing and clearly specify approval of the PGx assessments (ie, approval of Appendix 6). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate that approval of the PGx

assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments are not approved, then approval for the rest of the study will clearly indicate this and that PGx assessments will not be conducted.

10 Study Administration

Belimumab is under joint development by Human Genome Sciences, Inc. and GlaxoSmithKline Pharmaceuticals. Human Genome Sciences, Inc. is the sponsor of this study.

10.1 Informed Consent

A copy of the proposed informed consent document must be submitted to the sponsor or designee for review and comment prior to submission to the reviewing IRB/IEC. The consent form must be approved by the IRB/IEC and contain all elements required by national, state, local, and institutional regulations or requirements.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information using the IRB/IEC approved informed consent document(s), including the objective and procedures of the study and the possible risks involved before inclusion in the study. Each subject must voluntarily provide written informed consent (including consent for the use and disclosure of research-related health information). The consent must be obtained prior to performing any study-related procedures that are not part of normal patient care, including screening and changes in medications including any washout of medications. A copy of the signed informed consent must be given to the study subject.

10.2 Institutional Review Board Review/Independent Ethics Committee Review and Approval

The investigator or sponsor (as appropriate per national regulations) shall assure that an IRB/IEC, constituted in accordance with the ICH Guideline for Good Clinical Practice (GCP), will provide initial and continuing review of the study.

Prior to shipment of the study agent and enrollment of study subjects, documented IRB/IEC approval of the protocol, informed consent form, and any advertisement for subject recruitment must be obtained and provided to the sponsor or designee.

The IRB/IEC must also be informed of all protocol amendments prior to implementation. The investigator must provide reports of any change in research activity (ie, the completion, termination, or discontinuation of a study) to the IRB/IEC.

10.3 Protocol Compliance

Except for a change that is intended to eliminate an apparent immediate hazard to a study subject, the protocol shall be conducted as described. Any such change must be reported immediately to the sponsor and to the IRB/IEC.

10.4 Protocol Revisions

Protocol amendments will be prepared and approved by the sponsor. All protocol amendments will be signed by the investigator and submitted to the IRB/IEC for review prior to implementation. Documentation of IRB/IEC approval must be forwarded to the sponsor or designee. If an amendment significantly alters the study design, increases potential risk to the subject or otherwise affects statements in the informed consent form, the informed consent form must be revised accordingly and submitted to the IRB/IEC for review and approval. The approved consent form must be used to obtain informed consent from new subjects prior to enrollment and must be used to obtain informed consent from subjects already enrolled if they are affected by the amendment.

10.5 Data Collection and Management

The investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. The investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs, or tapes.

The anonymity of participating subjects must be maintained. For data collection and management purposes, subjects are to be identified by a subject number only. Documents that identify the subject beyond subject number will not be submitted to the sponsor (eg, the signed informed consent document; subject initials) and must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

Site personnel record all data for each study subject through electronic case report forms (eCRFs) using an Electronic Data Capture (EDC) system provided and approved by the sponsor. Refer to the Study Procedures Manual for additional information regarding CRFs that will be used as source documentation. Sites must complete the eCRFs in a timely manner and the investigator must promptly review the completed eCRFs for each subject. As the person ultimately responsible for the accuracy of all eCRF data, the investigator must sign the Investigator's Statement in each subject's eCRF.

The EDC system automatically generates queries resulting from the computer checks embedded into the system, so as to ensure accuracy, quality, consistency, and completeness of the database. Manual queries resulting from review by monitors, medical coders, and other Data Management staff are also generated from within the EDC system, where they are tracked. Sites resolve the queries and correct the entered data when necessary. Every change to data is captured in the EDC system audit trail. Upon completion of the study, or after reaching a pre-specified point in the study, Data Management will lock the database and generate the SAS datasets necessary for data analysis and reporting. Upon completion of the study, each site will be provided with a compact disc (CD) containing the eCRFs for each of their subjects.

10.6 Study Monitoring

The study sponsor or designee will monitor the study. Study monitors representing the sponsor will visit study sites routinely throughout the trial. The sponsor will review eCRFs and compare them with source documents to verify accurate and complete collection of data and confirm that the study is being conducted according to the protocol. Auditors representing the sponsor may also similarly evaluate the study and its monitors. For these purposes, the investigator will make eCRFs and source documents available when requested.

In addition, the study may be evaluated by representatives of the national regulatory authorities, who will also be allowed access to study documents. The investigators should promptly notify Human Genome Sciences of any audits they have scheduled with any regulatory authority.

10.7 Drug Accountability

Upon receipt of the study agents, the designated pharmacy personnel at the study site is responsible for taking an inventory of the study agent, including any buffers or diluents. A record of this inventory must be kept and usage must be documented on study agent inventory forms provided by the sponsor.

Study agent inventory forms will be examined and reconciled by a sponsor's blinded monitor, or designee. At the end of the study, all used and unused study agent must be accounted for on a study agent accountability form provided to the investigator by the sponsor or its designee.

10.8 Retention of Records

The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer discs or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the sponsor at the time the study is completed, terminated or discontinued.

If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the sponsor.

10.9 Financial Disclosure

The Investigator and all Sub-Investigators will provide the sponsor sufficient and accurate information on financial interests (proprietary or equity interests, payments exclusive of clinical trial costs) to allow complete disclosure to regulatory authorities. The investigators shall promptly update this information if any relevant changes occur during the course of the investigation and for a period of 1 year following study completion.

10.10 Publication Policy

This study is being conducted as part of a multi-center clinical study. Data from all sites participating in the multi-center clinical study will be pooled and analyzed. The investigator

acknowledges that an independent, joint publication is anticipated to be authored by the investigators of the multi-center study and sponsor's representatives. Neither institution nor principal investigator shall independently publish or present the results of the study prior to the publication of the multi-center study publication. The investigator agrees that the sponsor will be the coordinator and arbitrator of all multi-center study publications. For multi-center trials, no investigator will be authorized to publish study results from an individual center until the earlier of the multi-center trial results are published or 12 months after the end or termination of the multi-center trial at all sites.

The investigator shall submit a copy of any proposed publication, manuscript, abstract, presentation or other document with respect to this study to the sponsor for review and comment at least 60 days prior to its submission for publication or presentation. No publication or presentation with respect to the study shall be made unless and until all of the sponsor's comments on the proposed publication or presentation have been considered and any information determined by sponsor to be confidential information has been removed. If requested in writing by the sponsor, the investigator shall withhold material from submission for publication or presentation for an additional 60 days to allow for the filing of a patent application or the taking of other measures to establish and preserve the sponsor's proprietary rights.

10.11 Study or Study Site Termination

If the sponsor, the investigator, IRB/IEC or a regulatory authority discovers conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation between the sponsor and the investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the product.

The study site may warrant termination under the following conditions:

- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulatory authority regulations.
- Submission of knowingly false information from the research facility to the sponsor, study monitor, or the regulatory authority.
- Insufficient adherence to protocol requirements.

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List of Appendices

Appendix 1 American College of Rheumatology (ACR) Criteria for SLE

The ACR Criteria for the Classification of Systemic Lupus Erythematosus

(Tan et al, 1982, and Hochberg, 1997)

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

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

Appendix 2 International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Classification of Lupus Nephritis

CLASS I	**MINIMAL MESANGIAL LUPUS NEPHRITIS**
	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence.
CLASS II	**MESANGIAL PROLIFERATIVE LUPUS NEPHRITIS**
	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits.
	May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy.
CLASS III	**FOCAL LUPUS NEPHRITIS**
	Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving < 50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations.
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
CLASS IV	**DIFFUSE LUPUS NEPHRITIS**
	Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥ 50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥ 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥ 50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
CLASS V	**MEMBRANOUS LUPUS NEPHRITIS**
	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations.
	Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed.
	Class V lupus nephritis may show advanced sclerosis.
CLASS VI	**ADVANCED SCLEROSIS LUPUS NEPHRITIS**
	≥90% of glomeruli globally sclerosed without residual activity.

Adapted from:
Weening J, D'Agati V, Schwartz M, et al. The Classification of Glomerulonephritis in Systemic Lupus Erythematosus Revisited. J Am Soc Nephrol 2004; 15:241-150.

Appendix 3 SELENA SLEDAI Disease Assessment Scales

SELENA SLEDAI Score

Score if descriptor is present at time of visit or in the preceding 10 days.

Wgt.	Descriptor	Definition
8	Seizure	Recent onset (last 10 days). Exclude metabolic, infectious drug cause, or seizure due to past irreversible CNS damage.
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intellectual function with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	Visual Disturbance	Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate of hemorrhage in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes.
8	Cranial Nerve Disorder	New onset sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.
8	Lupus Headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
8	CVA	New onset of CVA(s). Exclude arteriosclerosis or hypertensive causes.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	Arthritis	More than 2 joints with pain & signs of inflammation (ie, tenderness, swelling or effusion).
4	Myositis	Proximal muscle aching/weakness associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	UrinaryCasts	Heme-granular or red blood cell casts.
4	Hematuria	> 5 red blood cells/high power field. Exclude stone, infection, or other causes.
4	Proteinuria	New onset or recent increase of more than 0.5 g/24 hours.
4	Pyuria	> 5 white blood cells/high power field. Exclude infection.
2	Rash	New or ongoing inflammatory lupus rash.
2	Alopecia	New or ongoing abnormal, patchy or diffuse loss of hair due to active lupus.
2	Mucosal Ulcers	New or ongoing oral or nasal ulcerations due to active lupus.
2	Pleurisy	Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.
2	Pericarditis	Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.
2	Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	Increased DNA Binding	> 25% binding by Farr assay or above normal range for testing laboratory.
1	Fever	> 38°C. Exclude infectious cause.
1	Thrombocytopenia	< 100,000 platelets/mm^3
1	Leukopenia	< 3,000 white blood cells/mm^3. Exclude drug causes.
	TOTAL SCORE	**(Sum of weights next to descriptors marked present)**

Adapted from:

Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI: a disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992; 35(6):630-40.

SLE Flare Index

Mild or Moderate Flare	Severe Flare
□ Change in SELENA SLEDAI instrument score of 3 points or more (but not to more than 12)	□ Change in SELENA SLEDAI instrument score to greater than 12
□ New/worse: Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus Nasopharyngeal ulcers Pleuritis Pericarditis Arthritis Fever (SLE)	□ New/worse: CNS-SLE Vasculitis Nephritis Myositis Plt < 60,000 Hemolytic anemia:Hb < 70 g/L or decrease in Hb > 30 g/L
□ Increase in prednisone, but not to > 0.5 mg/kg/day	**Requiring**: double prednisone, or prednisone increase to > 0.5 mg/kg/day, or hospitalization
□ Added NSAID or hydroxychloroquine for SLE Activity	□ Increase in prednisone to > 0.5 mg/kg/day
□ ≥1.0 increase in PGA score, but not to more than 2.5	□ New cyclophosphamide, azathioprine, methotrexate, or mycophenolate for SLE activity
	□ Hospitalization for SLE activity
	□ Increase in PGA score to > 2.5

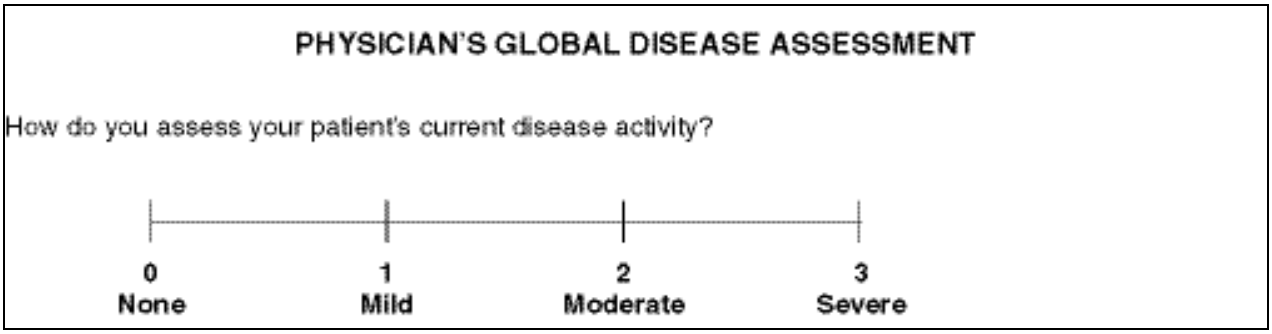
Adapted from:

Petri M, Buyon J, Kim M. Classification and definition of major flare in SLE clinical trials. Lupus 1999; 8:685-91.

Petri M et al. Combined Oral Contraceptives in Women with Systemic Lupus Erythematosus. N Engl J Med 2005;353:2550-8.

Buyon JP et al. The Effect of Combined Estrogen and Progesterone Hormone Replacement Therapy on Disease Activity in Systemic Lupus Erythematosus: A Randomized Trial. Ann Internal Med 2005; 142 (12 Pt 1):953-62.

Physician's Global Disease Assessment



Adapted from:

Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus 1999;8:685-91.

Appendix 4 SLICC/ACR Damage Index

Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus*

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

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

*Damage (nonreversible change, not related to active inflammation) occuring since onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

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

Appendix 5 Laboratory Tests

Hematology

Total white blood cell count
Differential:
- Absolute Neutrophils
  - Segmented Neutrophils
  - Band Neutrophils
  - Myelocytes
  - Metamylocytes
  - Promyelocytes
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Hemoglobin
Hematocrit
Red blood cell (RBC) count
Platelet count
Prothrombin time (PT)
Partial thromboplastin time (PTT)
Serum Pregnancy

Urinalysis

Protein
Glucose
Ketones
Occult blood
Microscopic examination including:
- WBC per hpf
- RBC per hpf
- Dysmorphic RBC
- Casts (specified by type eg, RBC, WBC)

Urine Pregnancy
Spot urine
24-hour urine
*When 24 hour urines are collected, the calculated GFR will be based on the mean value of two 24 hour urine and serum creatinine collections. For all other visits, the simplified MDRD formula will be used to estimate GFR and the spot urine method will be used for the proteinuria assessments. The urine microscopy and routine urinalysis will be performed locally. All other tests will be performed by a central laboratory.

Modified Chem-20

Electrolytes:
- Sodium
- Potassium
- Magnesium
- Chloride
- Carbon dioxide
- Calcium adjusted for Albumin
- Inorganic Phosphate

Enzymes:
- SGOT (AST)
- SGPT (ALT)
- Alkaline Phosphatase
- Gamma glutamyl transferase (GGT)
- Lactic dehydrogenase (LDH)

Other:
- Creatinine
- Blood urea nitrogen (BUN)
- BUN/creatinine ratio
- Bilirubin, total
- Protein, total

Albumin
- Uric acid
- Glucose

Infectious Disease Screening

HIV-1/2 antibody
Hepatitis C antibody
Hepatitis B surface antigen

Biological Markers

BLyS protein
Serum complement (C3 and C4)

FACS of peripheral lymphocytes: B lymphocytes ($CD20^+$, $CD20^+/27^+$ memory, $CD20^+/27^-$ naïve, $CD20^+/69^+$ activated, $CD20^+/138^+$ plasmacytoid, $CD19^+/27^{BRIGHT}/38^{BRIGHT}$ SLE subset $CD19^+/CD24^{HIGH}/CD38^{HIGH}$ regulatory B cell and $CD20^-/138^+$ plasma cells) Note: May be collected in selected sites/regions.

Autoantibodies

ANA
Anti-dsDNA
aCL (IgG, IgA and IgM isotypes)
Anti-Sm
Anti-c1q

Immunoglobulins

Serum immunoglobulin isotypes: IgG, IgM, IgA

Belimumab PK and Immunogenicity

Appendix 6 Pharmacogenetic Research

Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in different populations. There is increasing evidence that an individual's genetic composition (ie, genotype) may impact pharmacokinetics, pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability).

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Research Rationale

Blood samples for pharmacogenetics will be drawn as described in Section 9. Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analyses to be conducted if there is unexplained or unexpected variation in response to belimumab.

If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with belimumab that may be attributable to genetic variations of subjects, the following objectives may be investigated:

- Relationship between genetic variants and the pharmacokinetics of belimumab.
- Relationship between genetic variants and safety and/or tolerability of belimumab.
- Relationship between genetic variants and efficacy of belimumab.

Study Population

Any subject who has given informed consent to participate in the clinical study, has met all the entry criteria for the clinical study, and receives belimumab may take part in the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

Study Assessments and Procedures

In addition to any blood samples drawn for the clinical study, a whole blood sample (~10 mL) will be collected for the PGx research at baseline. The PGx sample is labeled (or coded) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample. The blood samples should be drawn on Day 0 (baseline), provided informed consent for PGx research has been obtained from the subject, but the sample may be taken at any time while the subject is participating in the clinical study.

If deoxyribonucleic acid (DNA) is extracted from the blood sample, the DNA will be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or set of studies) of belimumab has been completed and the study data reviewed. In some cases, the samples may not be studied.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or the sponsor may destroy the samples sooner. The sponsor or those working with the sponsor (for example, other researchers or a contract lab) will use samples collected from the study for the purpose stated in this protocol and in the subject informed consent form.

Subjects may request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research and has a sample taken for PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options:

1. The sample is retained for PGx research.
2. The sample is destroyed.

If a subject withdraws consent from the PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by the sponsor and maintain the documentation in the site study records. In either case, the sponsor will only use study information collected/generated up to that point.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by the sponsor and maintain the documentation in the site study records.

Pharmacogenetic Analyses

Specific sections of DNA may be selected from areas of the genome (ie, candidate genes). The candidate genes could include the drug target, the drug target pathway, drug metabolizing enzymes, genes associated with mechanisms underlying adverse events, and genes associated with the study disease.

In addition, a genome-wide scan or large scale sequencing of polymorphic markers located across the genome may be implemented. This approach is often employed when potential genetic effects are not well understood.

Other new technologies may be developed to help us better study and understand genetic variants associated with drug response.

Continuing research may identify other enzymes, transporters, proteins, or receptors that may be involved in response to belimumab. The genes that may code for these proteins may also be studied.

Components of the PGx analysis may include:

- Hardy-Weinberg Equilibrium testing

  The genotypic frequencies of each polymorphism will be evaluated for conformity to those expected under normal conditions by employing Hardy-Weinberg Equilibrium testing.

- Comparison of Demographic and Baseline Characteristics by Genotype

  Differences in baseline clinical characteristics and potential contributing covariates may be summarized and compared among genotype (or haplotype) subgroups.

- Evaluation of Genotypic Effects

  Analyses may be carried out to evaluate the degree of association between subject's genotype (or haplotype) and selected parameters (eg, pharmacokinetics, disease activity and safety). Where such genotypic tests are inappropriate (eg, where the number of marker genotypes is too large and/or the frequency of individual genotypes too small), allelic tests may be conducted. Allelic tests evaluate whether the frequency of each marker allele is the same in responders and non-responders.

- Evaluation of Treatment by Genotype and Gene-Gene Interaction

  In addition to evaluating the main effects of the genotypes (haplotypes or alleles) on the selected parameters, the possibility of a treatment group by genotype (haplotype or allele) interaction will also be explored. If appropriate, the joint effects of multiple markers (gene-gene interactions) may also be evaluated.

- Linkage Disequilibrium

  For pairs of polymorphisms, the degree to which alleles from the 2 sites are correlated (linkage disequilibrium) may also be evaluated. If the genotypes at 2 polymorphic sites within a gene are shown to be statistically associated with a response to study agent, the degree of linkage disequilibrium will aid interpretation in that it will indicate the extent to which the 2 sites are exerting independent effects.

- Multiple Comparisons and Multiplicity

  Adjustment to observed p-values may be made to limit erroneous conclusions due to multiple tests when multiple markers are evaluated (especially in the case of a genome scan for association).

- Power and Sample Size Considerations

  The ability to detect differential drug response among genotypes at a polymorphic site depends on the total number of subjects genotyped and the frequency distribution of the different genotypes. Consequently, genotyping analyses are plausible for those polymorphic sites where the number of subjects comprising the genotypic groups is sufficiently large; however, these frequencies will not be known until sufficient samples have been collected and genotyping is complete. These examples show that small sample sizes typically encountered in Phase 1 and Phase 2 studies may be sufficient to identify clinically relevant genetic associations.

Additional analyses may be conducted as necessary.

Provision of Study Results and Confidentiality of Subject's PGx Data

The sponsor may summarize the cumulative PGx research results in the clinical study report or in a separate report. In general, the sponsor does not inform the investigator, subject or anyone else (eg, family members, study investigators, primary care physicians, insurers, or employers) of the PGx research results because the information generated from PGx studies is preliminary in nature, and the significance and scientific validity of the results are undetermined at such an early stage of research, under any circumstance unless required by law.

Appendix 7 Adverse Event Severity Grading Tables

SKIN (INJECTION SITE)	GRADE 1 MILD	GRADE 2 MODERATE[1]	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Induration	< 15mm	15-30 mm	> 30mm	n/a
Erythema	< 15mm	15-30 mm	> 30mm	n/a
Edema	< 15mm	15-30 mm	> 30mm	n/a
Rash at Injection Site	< 15mm	15-30 mm	> 30mm	n/a
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	n/a

[1]May be assessed as mild despite the size if event is transient (< 48 hours) with mild discomfort; no medical intervention/therapy required

Modified from DMID Adult Toxicity Tables, 2007

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

(continued)

*ULN = Upper Limit of Normal.

Modified from DMID Adult Toxicity Tables, 2001

CARDIOVASCULAR	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cardiac Arrhythmia	-	Asymptomatic/transient; dysrhythmia; no treatment req	Recurrent/persistent dysrhythmia. Symptomatic; treatment req	Unstable dysrhythmia hospitalization and treatment required
Hypotension	Transient orthostatic hypotension, no treatment	Symptoms correctable with oral fluid treatment	IV fluid req, no hospitalization req	Hospitalization req
Hypertension	Transient, increase > 20 mm/Hg; no treatment	Recurrent; chronic increase > 20 mm/Hg, treatment req	Acute treatment req; out patient hospitalization possible	Hospitalization req
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion, pain, ECG changes	Tamponade OR pericardiocentesis OR surgery req
Hemorrhage, Blood Loss	-	Mildly symptomatic; no treatment required	Gross blood loss OR 1-2 units transfused	Massive blood loss OR > 2 units transfused

(continued)

Modified from DMID Adult Toxicity Tables, 2001

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

(continued)

Modified from DMID Adult Toxicity Tables, 2001

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

(continued)

*(Goldfarb et al, 2001; Yamani et al, 2001; Eibl and Rosen, 1995).

Modified from DMID Adult Toxicity Tables, 2001

GASTROINTESTINAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Nausea	Mild OR transient; reasonable intake maintained	Mod discomfort OR intake decreased for < 3 days	Severe discomfort OR minimal intake for ≥ 3 days	Hospitalization required
Vomiting	Mild OR transient; 2-3 episodes/day OR mild vomiting lasting < 1 week	Mod OR persistent; 4-5 episodes per day; OR vomiting lasting ≥ 1 week	Severe vomiting of all foods/fluids in 24 hours OR orthostatic hypotension OR IV treatment req	Hypotensive shock OR hospitalization required for IV treatment req
Diarrhea	Mild or transient; 3-4 loose stools per day OR mild diarrhea lasting < 1 week	Mod OR persistent; 5-7 loose stools per day or diarrhea lasting ≥ 1 week	Bloody diarrhea; OR orthostatic hypotension OR > 7 loose stools/day OR IV treatment req	Hypotensive shock OR hospitalization req
Oral Discomfort/Dysphagia	Mild discomfort, no difficulty swallowing	Difficulty swallowing but able to eat and drink	Unable to swallow solids	Unable to drink fluids; IV fluids req
Constipation	Mild	Moderate	Severe	Distention with vomiting

(continued)

Modified from DMID Adult Toxicity Tables, 2001

RESPIRATORY	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cough (for aerosol studies)	Transient; no treatment	Treatment associated cough; inhaled bronchodilator	Uncontrolled cough; systemic treatment req	-
Bronchospasm Acute	Transient; no treatment; FEV1 70% to < 80% (or peak flow)	treatment req; normalizes with bronchodilator; FEV1 50% to < 70% (or peak flow)	No Normalization with bronchodilator; FEV 25% to < 50% (or peak flow), retractions	Cyanosis; FEV1 < 25% (or peak flow) OR intubated
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring O2 therapy

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

(continued)

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

Modified from DMID Adult Toxicity Tables, 2001

MISCELLANEOUS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fever (oral > 12 hours)	37.7-38.5°C or 100.0-101.5°F	38.6-39.5°C OR 101.6-102.9°F	39.6-40.5°C OR 103-105°F	> 40.5°C OR > 105°F
Headache	Mild; No treatment req	Mod; or non-narcotic analgesia treatment	Severe; OR responds to initial narcotic treatment	Intractable; OR requiring repeated narcotic treatment
Allergic Reaction	Pruritus without rash	Localized urticaria	Generalized urticaria angioedema	Anaphylaxis
Cutaneous/Rash/ Dermatitis	Erythema, pruritus rash OR dry desquamation	Diffuse maculopapular OR dry desquamation	Vesiculation OR moist desquamation ulceration	ANY ONE: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, necrosis req surgery, exfoliative dermatitis
Local Reaction (secondary to parenteral treatment- not vaccination or skin test)	Erythema	Induration < 10 mm OR inflammation OR phlebitis	Induration > 10 mm OR ulceration	Necrosis of skin
Fatigue	Normal activity Reduced < 25%	Normal activity Reduced 25-50%	Normal activity reduced > 50%; cannot work	Unable to care for self

(continued)

Modified from DMID Adult Toxicity Tables, 2001

NEUROLOGIC	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuro-cerebellar	Slight incoordination OR dysdiadochokinesia	Intention tremor OR dysmetria OR slurred speech OR nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with ADLs	Unable to stand
Neuro-psych/ mood	-	none	Severe mood changes requires medical intervention	Acute psychosis requiring hospitalization
Paresthesia (burning, tingling, etc)	Mild discomfort; no treatment needed	Mod discomfort non-narcotic analgesia req	Severe discomfort; OR narcotic analgesia req with symptomatic improvement	Incapacitating; OR not responsive to narcotic analgesia
Neuro-motor	Mild weakness in muscle of feet but able to walk and/or mild increase or decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes), mild weakness in hands, still able to do most hand tasks and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop), and mod proximal weakness ie, in hands interfering with ADLs and/or requiring assistance to walk and/or unable to rise from chair unassisted	Confined to bed or wheelchair because of muscle weakness
Neuro-sensory	Mild impairment sensations, (ie, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment mod de-sensation, (ie, of vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical.	Severe impairment (dec or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (ie, upper and lower extremities)	Sensory loss involves limbs and trunk

(concluded)

Modified from DMID Adult Toxicity Tables, 2001

Appendix 8 Columbia- Suicide Severity Rating Scale (C-SSRS) Baseline/Screening

Columbia Suicide-Severity Rating Scale (C-SSRS)
Baseline/Screening

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.

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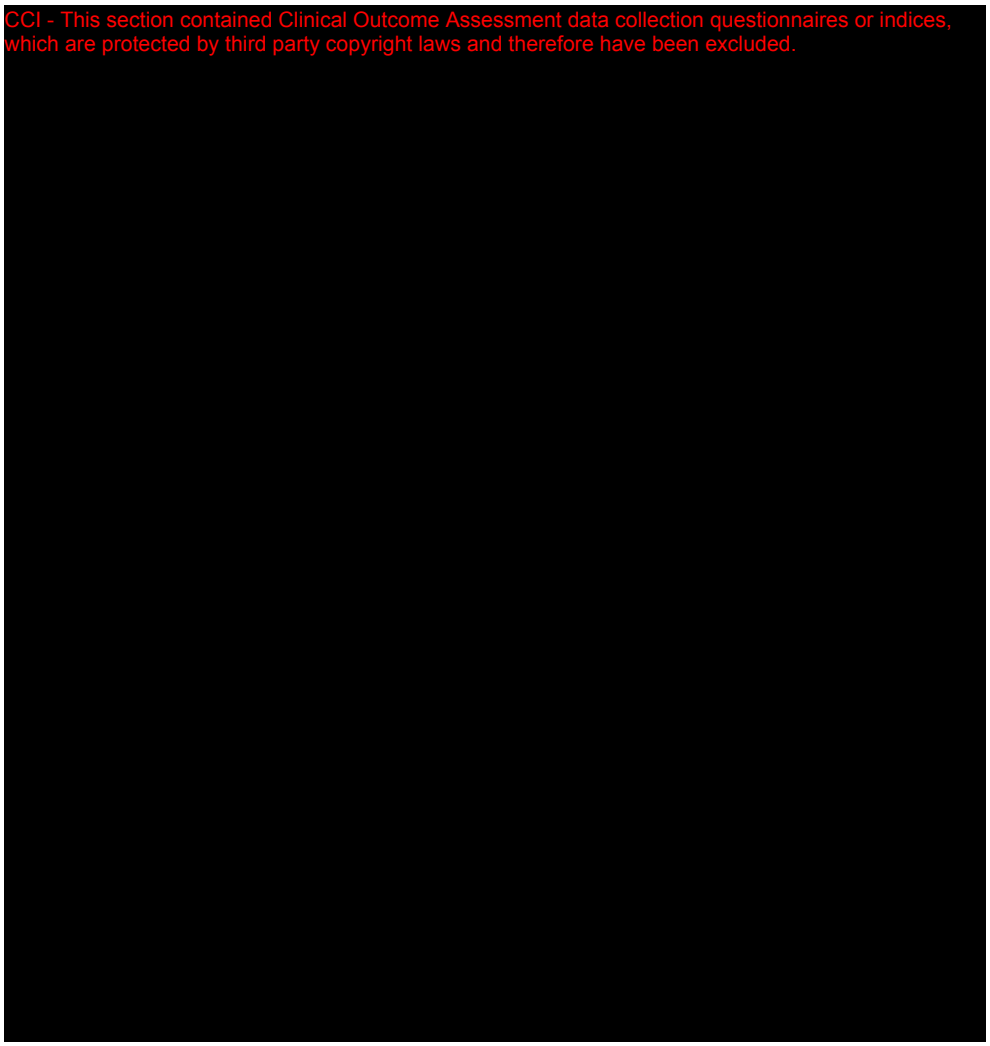
Appendix 9 Columbia- Suicide Severity Rating Scale (C-SSRS) Since Last Visit

Columbia Suicide-Severity Rating Scale (C-SSRS) Since Last Visit



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HGS Approval Page

PPD

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Senior Vice President,
Development and Regulatory Affairs

19 Oct 11

Date

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PPD MD

Executive Vice President,
Research and Development

19-Oct-11

Date