CLINICAL PROTOCOL HGS1006-C1112
Protocol Amendment: 02
Date: 09 February 2017
EudraCT Number: 2011-005672-42

TITLE OF STUDY:

A Phase 3/4, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Adult Subjects of Black Race with Systemic Lupus Erythematosus (SLE)

STUDY SPONSOR:

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Revision Chronology for HGS1006-C1112 (BEL115471)

	Date	**Document***
Global	21 November 2011	Original
Global	20 June 2012	Amendment No 01
Local 2014N219219_00	02 February 2015	Local Amendment No 01 for France
Global 2014N199062_00	09 February 2017	Amendment No 02

*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-C1112

Title of the Study: A Phase 3/4, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Adult Subjects of Black Race with Systemic Lupus Erythematosus (SLE).

Clinical Development Phase: 3/4

Objectives:

- To evaluate the efficacy of belimumab in adult SLE subjects of black race.
- To evaluate the safety and tolerability of belimumab in adult SLE subjects of black race.

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

1. Are at least 18 years of age.
2. Are of self-identified black race.
3. Have a clinical diagnosis of SLE according to the American College of Rheumatology (ACR) criteria (See Appendix 1).
4. Have active SLE disease defined as a SELENA SLEDAI score ≥ 8 at screening (refer to Appendix 5 and Section 6.8.1.1 Scoring for Proteinuria for Eligibility at Screening).
5. Have 2 unequivocally positive autoantibody test results defined as a positive antinuclear antibody (ANA) test [ie, a titer ≥ 1:80 by HEp-2 immunofluorescence assay (IFA) and/or positive enzyme immunoassay (EIA)] and/or a positive anti-dsDNA (≥ 30 IU/mL) serum antibody test as follows:
   - from 2 independent time points within the study screening period. Screening results must be based on the study's central laboratory results.

   OR

   - One positive historical test result and 1 positive test result during the screening period.
     - Historical documentation of a positive ANA test (eg, HEp-2 IFA or EIA) or anti-dsDNA (eg, anti-dsDNA by any validated commercial assay) must include the date and type of the test, the name of the testing laboratory, numerical reference range, and a key that explains values provided as positive vs negative OR negative, equivocal/borderline positive). Only unequivocally positive values as defined in the laboratory's reference range are acceptable; borderline values will not be accepted.
6. Are on a stable SLE treatment regimen consisting of any of the following medications (alone or in combination) for a period of at least 30 days prior to Day 0 (ie, day of 1st dose of study agent) [Refer to Section 5.5.1 for allowable medications and maximum dose]:

- Corticosteroids (prednisone or prednisone equivalent, up to 40 mg/day):
  - For subjects on SLE combination therapy, their stable steroid dose must be fixed within the range of 0 to 40 mg/day (prednisone or prednisone equivalent).
  - For subjects whose only SLE treatment is steroids, their stable steroid dose must be fixed within the range of 7.5 to 40 mg/day (prednisone or prednisone equivalent).
  - For those subjects on alternating day doses of steroids, use the average of 2 daily doses to calculate the average daily steroid dose.
- Other immunosuppressive or immunomodulatory agents including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), calcineurin inhibitors (eg, tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine, mizoribine, or thalidomide.
- Anti-malarials (eg, hydroxychloroquine, chloroquine, quinacrine).
- Non-steroidal anti-inflammatory drugs (NSAIDs).

NOTE:

- Pre-existing SLE medications must be stable for at least 30 days prior to Day 0.
- Corticosteroids may be added as new medication or their doses adjusted only up to 30 days prior to Day 0 (see Exclusion Criterion #6).
- New SLE therapy other than corticosteroids must not be added within 60 days of Day 0 (see Exclusion Criterion #5).

7. A female subject is eligible to enter the study if she is:
   - Not pregnant or nursing;
   - Of non-childbearing potential defined as
     - pre-menopausal females with a documented tubal ligation, hysterectomy, documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion, or documented bilateral oophorectomy or
     - postmenopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile [eg, > 45 years, in the absence of hormone replacement therapy or other cause for amenorrhea]; in questionable cases obtain a blood sample for follicle stimulating hormone (FSH) and estradiol simultaneously to confirm. Diagnostic levels for FSH and estradiol vary by specific laboratories/assays;
   - OR is of child-bearing potential with negative pregnancy test as determined by serum human chorionic gonadotrophin (hCG) test at screening and urine hCG test prior to dosing AND
     - Agrees to use one of the contraception methods listed in the protocol (see Section 4.3) for 2 weeks prior to the day of dosing to sufficiently minimize the

risk of pregnancy at that point. Female subjects must agree to use contraception until 16 weeks following the last dose of study agent.

- OR has only same-sex partners, when this is her preferred and usual lifestyle.

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. Have received treatment with anti-BLyS [belimumab]) at any time.
2. Have received any of the following within 364 days of Day 0:
   - Abatacept.
   - Other B cell targeted therapy (eg, rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI-Fc, or anti-BAFF (LY2127399).
   - A biologic investigational agent other than B cell targeted therapy (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.)
3. Have required 3 or more courses of systemic corticosteroids for concomitant conditions (eg, asthma, atopic dermatitis) within 364 days of Day 0. (Topical or inhaled steroids are permitted.)
4. Have received any of the following within 90 days of Day 0:
   - Anti-TNF therapy (eg, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab).
   - Intravenous (IV) cyclophosphamide.
   - Interleukin-1 receptor antagonist (anakinra).
   - Intravenous immunoglobulin (IVIG).
   - High dose prednisone or equivalent (> 100 mg/day).
   - Plasmapheresis.
5. Have received any of the following within 60 days of Day 0:
   - A non-biologic investigational agent.
   - Any new immunosuppressive/immunomodulatory agent, anti-malarial, or NSAID (see Inclusion Criterion #6).
     - Note: New inhaled and topical steroids and new topical immunosuppressive agents (eg, eye drops, topical creams) are allowed. Any NSAID use for < 1 week is allowed.
   - Any steroid injection (eg, intramuscular, intraarticular, or intravenous).

6. Have received any of the following within 30 days of Day 0:
   - A live vaccine.
   - A change in dose of a corticosteroid, other immunosuppressive/immunomodulatory agent, anti-malarial, or NSAID (see Inclusion Criterion #6).
7. Have severe lupus kidney disease (defined by proteinuria > 6 g/24 hour or equivalent using spot urine protein to creatinine ratio, or serum creatinine > 2.5 mg/dL), or have severe active nephritis requiring acute therapy not permitted by protocol (eg, IV cyclophosphamide within 90 days of Day 0), or have required hemodialysis or high-dose prednisone or equivalent (> 100 mg/day) within 90 days of Day 0.
8. Have severe active central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident [CVA], cerebritis, or CNS vasculitis) requiring therapeutic intervention within 60 days of Day 0.
9. Have a history of a major organ transplant (eg, heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant.
10. 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.
11. 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.
12. 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.
13. 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 Day 0.
    - Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of Day 0.
14. 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) (refer to Appendix 3 for baseline/screening C-SSRS) in the last 2 months or who, in the investigator's opinion, pose a significant suicide risk.
15. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 0.
16. Have a historically positive test or test positive at screening for HIV antibody, hepatitis B surface antigen (HBsAg), hepatitis B core antibody, or hepatitis C antibody.
17. Have an IgA deficiency (IgA level < 10 mg/dL).

18. Have a Grade 3 or greater laboratory abnormality based on the Adverse Event Severity Grading Tables (Appendix 12) except for the following that are allowed:
    - Stable Grade 3 prothrombin time (PT) secondary to anticoagulant, eg, 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 3/4 proteinuria (≤ 6 g/24 hour equivalent by spot urine protein to creatinine ratio allowed).
    - Stable Grade 3 hypoalbuminemia due to lupus nephritis, and not related to liver disease or malnutrition.
    - 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 ALT and/or AST must be ≤ Grade 2.
    - Stable Grade 3 neutropenia or stable Grade 3 white blood cell count.
    - Stable Grade 3 hemoglobin reduction due to lupus.
19. Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins, or monoclonal antibodies.

Study Design and Schedule:

This is a Phase 3/4, multi-center, international, randomized, double-blind, placebo-controlled, 52-week study to evaluate the efficacy and safety of belimumab in adult subjects of black race with active SLE. Approximately 501 SLE subjects will be randomized with a target of at least 334 subjects receiving belimumab and 167 subjects receiving placebo.

In addition to receiving stable standard therapy, subjects will be randomized in a 2:1 ratio to treatment with either 10 mg/kg belimumab or placebo. At randomization, subjects will be stratified by their screening SELENA SLEDAI score (8-9 vs ≥ 10), complement level (C3 and/or C4 low vs other), and region (US/Canada vs rest of the world). Subjects will be dosed with study agent on Days 0, 14, 28, and then every 28 days through 48 weeks, with a final evaluation at Week 52 (4 weeks after the last dose). Study agent will be administered intravenously (IV) over no less than 1 hour. Subjects will remain under clinical supervision for 3 hours after completion of the first 2 infusions during the 52-week double-blind phase and 6-month open-label extension.

All subjects will continue the stable standard therapy they were receiving during the screening period. Subjects who complete dosing up to 48 weeks will return for a Day 364/Week 52 (final evaluation) visit. Subjects who successfully complete the initial 52 week double-blind phase may enter into a 6-month open-label extension. The Day 364/Week 52 visit will serve as the Day 0 visit for subjects entering the 6-month open-label extension. Subjects on active drug or placebo will receive belimumab 10 mg/kg IV every 28 days for 6 months in the open-label extension. The 1st dose on the 6-month open-label extension will be given on Day 364 (Week 52) of the double-blind treatment phase following the completion of all Day 364 (Week 52) assessments. Subjects participating in the 6-month open-label extension will continue to be monitored for safety

and more latitude will be permitted for background medication changes as outlined in Section 5.5.

At the end of the 6-month open-label period, subjects who 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 a separate continuation protocol. 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 separate continuation protocol. Subjects who complete the 52-week double-blind phase, but do not enter the 6-month open-label extension will be required to return for an additional follow up visit 8 weeks after the last dose of study agent. Subjects who withdraw early will be required to return for an Exit visit (4 weeks after the last dose of study agent) and a follow-up visit approximately 8 weeks after their last dose of study agent. In the event that a subject discontinues study agent at any time during the study or withdraws consent, an attempt will be made to ascertain survival status approximately 52 weeks after the first dose of study agent.

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

Efficacy Endpoints and Analysis:

The primary efficacy endpoint is the systemic lupus erythematosus responder index (SRI) response rate with the modified SLEDAI-2K scoring for proteinuria at Week 52.

A SRI response is defined as:

- ≥ 4 point reduction from baseline in SELENA SLEDAI score (with the modified SLEDAI-2K scoring for proteinuria),

AND

- No worsening (increase of < 0.30 points from baseline) in Physician's Global Assessment (PGA),

AND

- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (ie, at Week 52).

Major secondary efficacy endpoints:

1. SRI response rate with the SELENA SLEDAI for scoring of proteinuria at Week 52.
2. Time to first severe flare (as measured by the modified SLE Flare Index; with SLEDAI-2K and SELENA SLEDAI as the SLEDAI criterion of the SFI).
3. Percent of subjects whose average prednisone dose has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52, in subjects receiving greater than 7.5 mg/day at baseline.

Sample Size Calculation:

Approximately 501 subjects will be randomized and treated in the study, with a target of at least 334 subjects in the arm receiving belimumab and 167 subjects in the arm receiving placebo. This sample size provides at least 90% power at a 5% level of significance to detect a minimum of a 15.55% absolute improvement in the SRI response rate with the modified SLEDAI-2K scoring for proteinuria for the 10 mg/kg belimumab group relative to the placebo group (assumed rate = 43.95%) at Week 52. This sample size is also sufficient to provide approximately 80% power at a 5% level of significance to detect a minimum of a 13.4% absolute improvement in the SRI response rate with the SELENA SLEDAI scoring for proteinuria for the 10 mg/kg belimumab group relative to the placebo group (assumed rate = 44.8%).

The selection of these assumed treatment differences is based on the observed SRI data from studies BEL112341 (HGS1006-C1115/BLISS SC) and BEL113750 (Northeast Asia), which are two efficacy studies that concluded in 2015 and 2016, respectively, and have nearly identical eligibility criteria to study HGS1006-C1112 including requiring a screening SS score ≥8.

Analysis of Primary Efficacy Endpoint:

The proportion of subjects achieving a treatment response at Week 52 will be compared between the belimumab treatment group and placebo using a logistic regression model, adjusted for baseline randomization factors. The independent variables in the model will include treatment groups (ie, belimumab vs placebo), baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), complement level (C3 and/or C4 low vs other), and region (US/Canada vs rest of the world). However, the adjustment will not occur for any of these baseline randomization factors that has < 10 responders or < 10 non-responders in a stratification level (Peduzzi et al, 1996). The analysis will be performed on an intention-to-treat (ITT) population, defined as all subjects who are randomized and treated with 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.

Any subject who withdraws from the study prior to the Day 364 (Week 52) visit, misses the Day 364 (Week 52) visit (± 28 day window allowed), and/or starts a prohibited medication or dose prior to the Day 364 (Week 52) visit will be considered a non-responder for the Week 52 primary efficacy analysis.

Analysis of Major Secondary Efficacy Endpoints:

The SRI response rate with the SELENA SLEDAI scoring for proteinuria at Week 52 will be compared between the belimumab treatment group and the placebo group using the same analysis methods as described for the primary endpoint.

The time to the 1st severe SLE flare over 52 weeks will be compared between the belimumab treatment group and the placebo group using the Cox proportional hazard model. The independent variables in the model will include treatment groups (ie, belimumab vs placebo), baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), complement level (C3 and/or C4 low vs other), and region (US/Canada vs rest of the world). However, this adjustment will not occur for any of these baseline randomization factors that has < 10 events (severe flares) or < 10 non-events in a stratification level. If a subject withdraws from the study or completes the study up to the Day 364 (Week 52) visit without any severe SLE flare, time to the 1st severe SLE flare will be censored at the time of the last observation. If a subject receives a dose of protocol prohibited/restricted medication that results in treatment failure designation up to the Week 52 visit, the subject will be considered as having a severe SLE flare at the time the medication is started.

The percent of subjects with average prednisone dose that has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52 will be compared between the belimumab treatment and the placebo groups using a logistic regression model. The independent variables in the model will include treatment groups (ie, belimumab vs placebo), baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), complement level (C3 and/or C4 low vs other), and region (US/Canada vs rest of the world). However, the adjustment will not occur for any of these baseline randomization factors that has < 10 events (ie, having a prednisone reduction by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52) or < 10 non-events in a stratification level. The analysis will be performed on subjects who used prednisone > 7.5 mg/day at baseline. Any subject who withdraws from the study prior to the Day 364 (Week 52) visit, misses the Day 364 (Week 52) visit, and/or receives a dose of protocol prohibited/restricted medication that results in treatment failure designation prior to the Day 364 (Week 52) visit will be considered as without any prednisone reduction for the analysis.

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 belimumab treatment groups.

An Independent Data Monitoring Committee (IDMC) will review unblinded safety data for this study on an ongoing basis until the data are locked and analyzed through Week 52. The IDMC will include at least 3 physicians, and a statistician, none of whom are

affiliated with the sponsor. 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. The 1st IDMC data review meeting will occur after the first 100 subjects have been treated through Day 56 or within 6 months of the treatment of the 1st subject, whichever is earlier. After the initial review, the committee will review the data approximately every 6 months. Investigators and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), as appropriate, will be notified of the outcome of each IDMC meeting.

PK 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 on Days 0, 56 (Week 8), 168 (Week 24), 364/Exit (Week 52), and at the 8-week follow-up visit.

Biological Markers and Autoantibodies:

The following biological markers will be measured at baseline (Day 0) and at multiple time points thereafter:

- Autoantibodies: anti-dsDNA, anti-phospholipid antibodies (aCL, lupus anticoagulant, ± beta-2-glycoprotein-1), and extractable nuclear antigens (ENAs).
- ANA (baseline).
- Serum immunoglobulin isotypes: IgG, IgM, IgA.
- Serum complement (C3, C4).
- BLyS protein (baseline).

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

- 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, $CD19^+/24^{HIGH}/38^{HIGH}$ regulatory B cells, and $CD20^-/138^+$ plasma cells).

Study Calendar:

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

Study Schematic:

See Figure 0-1.

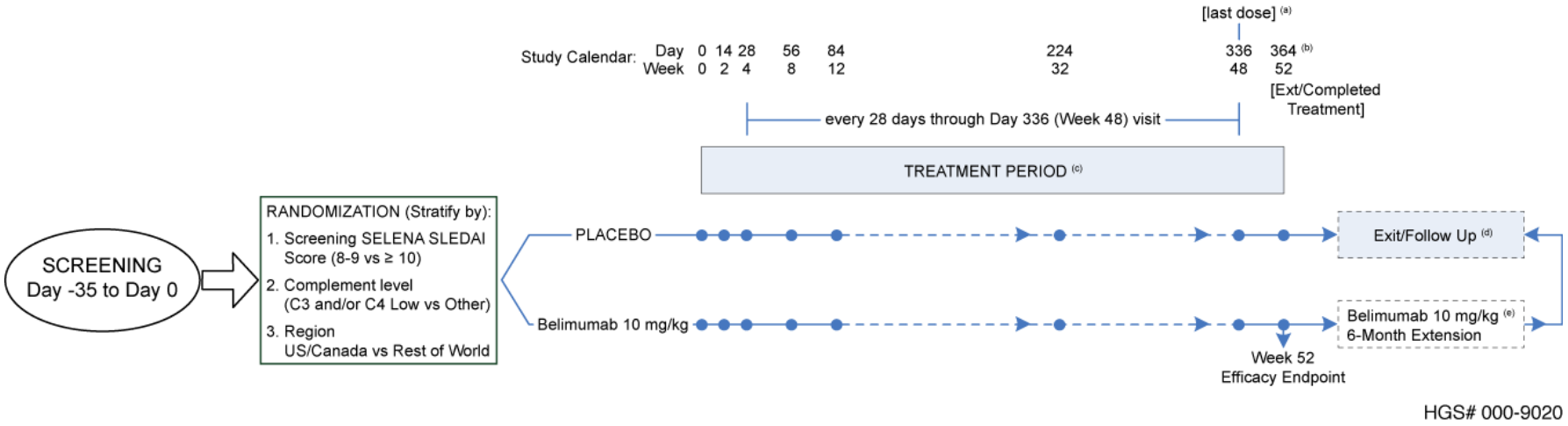

Figure 0-1 Study schematic

a The last dose of study agent is given on the Day 336 (Week 48) visit to subjects NOT participating in the 6-month open-label extension.

b Subjects participating in the 6-month open-label extension phase of the study are dosed on the Day 364/Week 52 visit of the double-blind period after the completion of all Day 364/Week 52 assessments. This Day 364/Week 52 represents the first dose (ie, Day 0) of the 6-month open-label extension. For subjects not participating in the 6-month open-label extension, the Day 364/Week 52 visit serves as the Exit visit, with follow-up visit occurring 8 weeks after the last dose of study agent.

c The primary treatment period includes 48 weeks of study agent administration (Day 0 to the Day 336 visit) **and** a final visit for the primary endpoint assessment at Week 52 which is 4 weeks after the last dose of the study agent.

d An Exit visit (1-4 weeks after the last dose of study agent) and a follow-up visit 8 weeks after the last dose of study agent will be performed for subjects withdrawing at any time during the study. The 8-week follow-up visit is not required in subjects entering the separate continuation protocol.

e At the end of the 6-month extension period, subjects who wish to continue treatment may do so by being prescribed the commercially available IV belimumab. If IV belimumab is not commercially available in a subject's country of participation, subjects may continue to receive belimumab administered IV every 4 weeks under a separate continuation protocol.

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aCL	anticardiolipin
ACR	American College of Rheumatology
AE	adverse event
ANA	anti-nuclear antibody
ANCOVA	analysis of covariance
Anti-dsDNA	anti-double-stranded DNA
Anti-TNF	anti-tumor necrosis factor
ARB	angiotensin receptor blocker
AUC	area under the serum drug concentration-time curve
BAFF	B-cell activating factor
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	cluster of differentiation
Cl_{cr}	creatinine clearance
CNS	central nervous system
COX	cyclooxygenase
CrCl	creatinine clearance
CRF	case report form
CRO	Contract Research Organization
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CVA	cerebrovascular accident
DI	damage index
dL	deciliter
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DO=F	dropout = failure
dsDNA	double stranded DNA
DSM	Diagnostic and Statistical Manual
ECL	electrochemiluminescence
eCRF	electronic case report form
EDC	electronic data capture
EIA	Enzyme immunoassay
ELISA	enzyme linked immunosorbent assay
ENA	extractable nuclear antigens
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FACS	florescence activated cell sorting
Fc	immunoglobulin constant region (fragment crystallizable)
FDA	United States Food and Drug Administration
g	gram
GCP	Good Clinical Practice

GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
HB	Hepatitis B
HBsAg	Hepatitis B surface antigen
hCG	human chorionic gonadotrophin
HEp-2	human epithelial cell line 2
HGS	Human Genome Sciences, Inc.
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
Hpf	high power field
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFA	immunofluorescence assay
Ig	immunoglobulin
IM	intramuscular
IRB	Institutional Review Board
ITT	intention to treat
IUD	intrauterine device
IV	intravenous
IVIG	intravenous immunoglobulin
IVRS	interactive voice response system
IWRS	interactive web response system
JVC	John Cunningham virus
kg	kilogram
LDH	lactic dehydrogenase
LOCF	last observation carried forward
MCID	minimal clinically important difference
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intention to treat
MMF	mycophenolate mofetil
µg	microgram
mg	milligram
µL	microliter
mL	milliliter
NS0	mouse myeloma cell line
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NSAIDs	non-steroidal anti-inflammatory drugs
NWHIC	National Women's Health Information Center
OD	optical density
OMHRC	Office of Minority Health Resource Center
PASS	Power Analysis and Sample Size
PGA	Physician's Global Disease Assessment

PGx	pharmacogenetics
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PO	*per os* (by mouth)
PSRQ	possible suicidality related questionnaire
PSRHQ	possible suicidality related history questionnaire
PT	prothrombin time
PTT	partial thromboplastin time
QOL	quality of life
RA	rheumatoid arthritis
RBC	red blood cell
SAE	serious adverse event
SC	subcutaneous
scFv	single chain antibody
SD	standard deviation
SELENA	Safety of Estrogen in Lupus National Assessment trial
SFI	SELENA flare index
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
$t_{1/2,term}$	terminal half-life
TNF	tumor necrosis factor
ULN	upper limits of normal
US	United States of America
USAN/INN	United States adopted name/international nonproprietary name
WBC	white blood cell

1. BACKGROUND

1.1. Disease Background

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). The disease onset is generally between the ages of 20 and 40 years. 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).

The current paradigm of the pathogenesis of SLE begins with a genetic predisposition (multi-factorial as > 10 chromosomal regions have been identified) that leads to the production of pathogenic autoantibodies, cytokine abnormalities, and autoreactive effector B and T lymphocytes (Harley et al, 1998; Lipsky, 2001; Schur, 1995). B lymphocyte abnormalities include an altered state of B lymphocyte differentiation, indicated by increased numbers of plasma cells secreting immunoglobulin (Ig), especially during times of increased clinical activity (Grammer and Lipsky, 2003). B lymphocytes isolated from SLE patients often have dysregulated expression of cell surface molecules, such as B7 and CD40, suggesting an enhanced state of B lymphocyte activation (Yazdany and Davis, 2004).

The behavior of laboratory biomarkers in SLE is under active investigation (Illei et al, 2004a; Illei, 2004b; Schiffenbauer et al, 2004). As yet, no clear surrogate endpoints have been widely accepted that clearly define clinical outcomes for the multi-organ system manifestations of SLE. As such, it is important to evaluate multiple markers of disease activity which may be clinically meaningful. Autoantibodies have been shown to be important early markers of specific disease processes or severity in SLE (Hahn, 1998; Leslie et al, 2001; Ravirajan et al, 2001) and are associated with disease activity (Villarreal et al, 1997). Autoantibodies can be directly involved in the disease process by binding to their target antigen and initiating immune injury by triggering a cascade of cellular and cytokine responses or indirectly, through immune complex

formation (Kotzin, 1996; Macchi et al, 1997). Many of the specific autoantibodies associated with autoimmune diseases appear to be antigen selected and require T lymphocyte help associated with conventional B lymphocyte antibody responses (Ando et al, 1987; Hahn, 1998). Patients with active general or organ-specific SLE may have distinct autoantibody profiles (Villarreal et al, 1997). The mechanism for initiation of these autoantibody responses is unclear. However, prolonged survival of B lymphocytes, molecular mimicry, altered tolerance to self-antigens, and abnormal apoptosis have been proposed as potential triggering mechanisms (Hutloff et al, 2004).

Standard therapies for SLE include corticosteroids (the mainstay of therapy), anti-malarial agents (eg, hydroxychloroquine), non-steroidal anti-inflammatory drugs (NSAIDs), cytotoxic agents like cyclophosphamide, and immunosuppressive/immunomodulatory agents used in cancer or transplantation (eg, azathioprine, cyclosporine, mycophenolate mofetil (MMF), methotrexate, leflunomide, thalidomide, 6-mercaptopurine). (Brocard et al, 2005; Chatham and Kimberly, 2001; Ginzler et al, 2005; Houssiau et al, 2004; Petri, 2001; Reveille, 2001; Ruiz-Irastorza et al, 2001; Wallace, 2002). These therapies can be associated with significant toxicity. Long-term use of high-dose corticosteroids can cause significant morbidity including osteoporosis, osteonecrosis, metabolic disorders (including exacerbation of diabetes), increased infection risk, edema, weight gain, and hyperlipidemia (Chatham and Kimberly, 2001). Cytotoxic agents like cyclophosphamide are immunosuppressive, resulting in increased risk of serious infections and certain cancers. Belimumab (also known as BENLYSTA™) is also approved in the United States (US), Canada, and the 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 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 pharmacologic, pharmacokinetic (PK), and toxicologic data generated with belimumab are provided in the Investigator's Brochure (IB).

1.2.2. Clinical Experience with Belimumab Administered Intraveneously

Belimumab administered as an IV infusion in SLE patients has been studied 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). Belimumab administered by subcutaneous injection is also being evaluated in clinical trials.

Phase 3 studies of belimumab administered IV in SLE were completed in 2009 and 2010 and formed the basis of the approval of 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 were also observed. Treatment with belimumab plus standard therapy 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 therapy 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 patients 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.

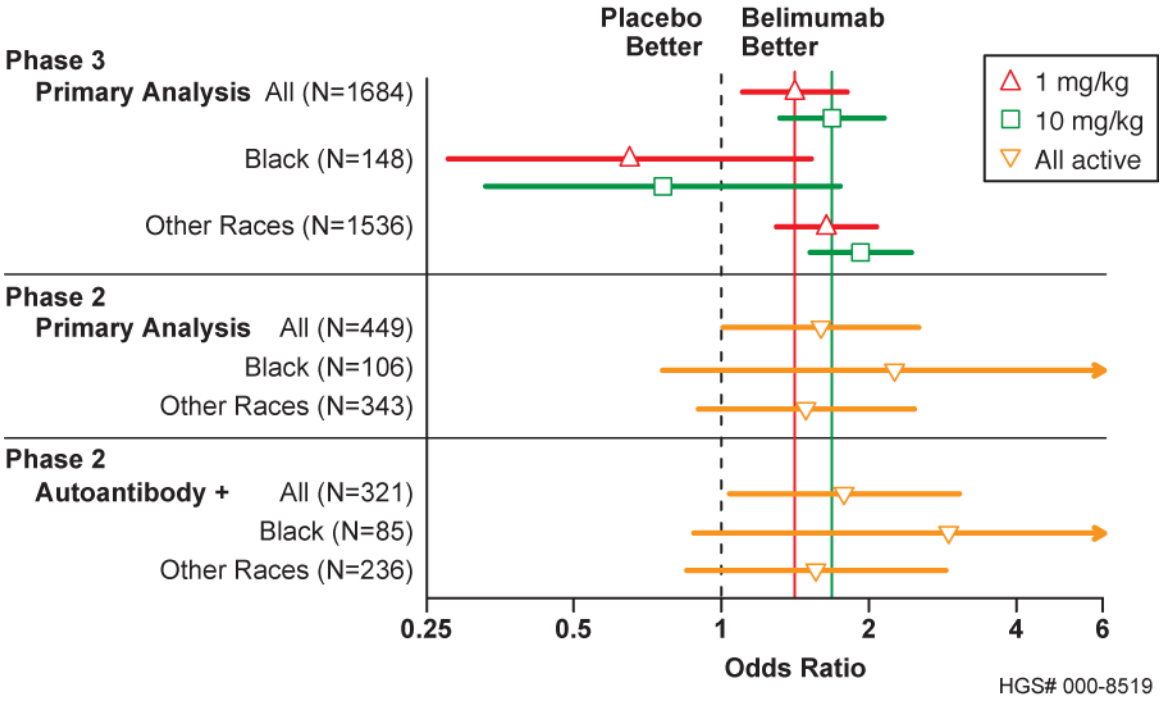
1.3. Rationale for the Study

1.3.1. General Rationale

Univariate and multivariate subgroup analyses of the primary efficacy endpoint (SRI at Week 52) were performed on the pooled Phase 3 study results. Although treatment-by-race did not trigger an interaction p-value < 0.10 in these analyses, among black subjects [N = 148; 80% of whom participated in BLISS 76 (C1056)], response rates were higher in the placebo plus standard therapy group than they were in the belimumab plus standard therapy groups. Belimumab had similar effects on biomarkers (autoantibodies, complement, and B cell subsets) in black subjects compared with other subjects.

While an apparent lack of benefit was observed in black subjects in Phase 3, the opposite was observed in the Phase 2 study, where black subjects (N = 106) had a better response to belimumab than non-black subjects. The treatment effect shown as odds ratios in the black and non-black subgroups in Phase 3 and Phase 2 is shown in Figure 1-1. The reasons for the different results in black subjects in Phase 3 vs Phase 2 are unknown. Baseline characteristics were similar in black subjects in Phase 2 and Phase 3. The numbers of black subjects in the Phase 2 and Phase 3 studies are too small to draw conclusions about observed treatment differences and therefore further study is needed.

Figure 1-1 Treatment effect in black subgroup in Phase 3 vs Phase 2 (SRI at Week 52)



The univariate and multivariate analyses suggested that subjects with higher disease or serological activity, as measured by SELENA SLEDAI scores ≥ 10, greater steroid use and low complement appeared to benefit from belimumab treatment most. Consistent with this finding, black subjects with higher disease activity (SELENA SLEDAI scores of at least 10) appeared to derive greater benefit with belimumab treatment.

Importantly, the safety profile in black subjects receiving belimumab was similar to those receiving placebo. Although black subjects reported more serious and severe adverse events than non-black subjects, the rates were similar between the belimumab and placebo groups. There were more discontinuations due to an adverse event in the black subgroup than in other races, with a greater rate in the belimumab groups (Table 1-1).

Table 1-1 Safety in black subgroup vs all other races

	Black/African American			All Others		
	Placebo N = 74 (%)	1 mg/kg N = 72 (%)	10 mg/kg N = 78 (%)	Placebo N = 601 (%)	1 mg/kg N = 601 (%)	10 mg/kg N = 596 (%)
At least 1 AE	93.2	97.2	93.6	92.3	92.5	92.6
Serious AE	28.4	19.4	24.4	14.3	18.5	16.4
Severe AE	27.0	19.4	21.8	14.0	15.0	14.4
Serious and/or Severe AE	33.8	26.4	29.5	20.0	22.6	21.6
Discontinuation due to AE	9.5	12.5	11.5	6.8	5.5	6.0

The small numbers of subjects, and conflicting results, do not allow conclusions to be drawn with respect to the efficacy of belimumab in subjects of black race. The available data suggests that belimumab has an acceptable safety profile in this population. Given that black subjects are disproportionately affected by SLE, both in terms of frequency and severity, it is important that the efficacy and safety of belimumab be fully evaluated in this population. This multi-center, randomized, double-blind, placebo-controlled, 52-week study is intended to evaluate the efficacy and safety of IV administered belimumab in adult subjects of black race (self-identified) with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy.

1.3.2. Choice of Target Patient Population

Black race is associated with higher prevalence rates of lupus disease, higher overall disease activity, increased overall end-organ damage, and higher mortality rates compared to Caucasians (Johnson et al, 2006; Uribe and Alarcon, 2003).

The target population to be enrolled in this trial will be adult subjects of self-identified black race with a clinical diagnosis of SLE according to the ACR criteria. These subjects must have active disease defined as a SELENA SLEDAI score ≥ 8 at screening, and be positive for autoantibodies, defined as a positive ANA test, and/or anti-dsDNA (≥ 30 IU/mL) at 2 time points prior to randomization. A minimum SELENA SLEDAI score of 8 and a positive diagnosis by the ACR criteria (at least 4 of 11 manifestations of SLE)

will ensure enrollment of an SLE population with active disease. Subjects in the Phase 3 trials with SELENA SLEDAI scores ≥ 7 had higher response rates to belimumab.

1.3.3. Rationale for Choice of Primary Endpoint for Efficacy

The primary efficacy endpoint is response by the SLE responder index (SRI) response rate with the modified SLEDAI-2K scoring for proteinuria at Week 52. It is evidence-based and supported by the data from the Phase 2 (LBSL02) and Phase 3 (HGS1006-C1056 and C1057) SLE trials. This was the primary efficacy endpoint in the Phase 3 trials of belimumab IV. The SRI includes an objective measure of the reduction in global disease activity (reduction in SELENA SLEDAI score ≥ 4) and 2 measures to ensure that the improvement in disease activity is not offset by worsening of the subject's condition overall (ie, no worsening in the PGA defined as an increase of < 0.3 points) or worsening in any specific organ system (ie, no new BILAG A or 2 new B organ domain scores).

1.3.4. Rationale for Dose and Schedule

The dose and schedule to be studied is 10 mg/kg administered as an IV infusion over no less than 1 hour, at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

In the Phase 3 trials supporting approval of belimumab in the US, Canada, and EU, only the 10 mg/kg dose achieved the primary endpoint in both Phase 3 IV trials, although both 1 mg/kg and 10 mg/kg belimumab were active. The SRI (including prespecified and post-hoc sensitivity analyses), severe flare risk reduction, and normalization of complement all favored the 10 mg/kg dose. While reductions in steroid dose favored 1 mg/kg, fewer patients receiving 10 mg/kg belimumab required increases in steroid dose. Certain B cell subsets, including plasma cells, short-lived plasma cells, and $CD19^{+}/CD27^{BRIGHT}/CD38^{BRIGHT}$ B cells, also showed trends for a dose response favoring 10 mg/kg. Importantly, there was no consistent pattern of dose-related adverse findings. The totality of the data supported approval of the 10 mg/kg dose of belimumab in the US, EU, and Canada, and approvals in other countries are being sought.

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 non opportunistic infections. Potential risks (ie, 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, 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 dyspnoea. However, infusion and hypersensitivity reactions can be severe and fatal. Most clinical trial and spontaneous cases of serious hypersensitivity occurred during or within the first hour after the completion of the infusion, although some cases report delayed acute onset (>4 hours but <4 days) or a delayed non-acute onset (4-21 days) hypersensitivity reactions.

Infections have been reported with administration of belimumab and are also associated with both SLE and immunosuppressant medication used to treat SLE. The mechanism of action of belimumab may increase the potential risk for the development of infections. In the phase 2 and 3 clinical trials, there was a slight increase in the overall rate of infections in the belimumab group compared with the placebo group. There was no difference in the rate of serious infections, infections leading to discontinuation, or infections of special interest. Out to 10 years in the Phase 2 and 3 continuation studies, the incidence rate of serious infections has remained stable or declined over time.

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. Delays 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.
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	Exclude patients with any of the following: currently on any suppressive therapy for a chronic infection; hospitalization for treatment of an infection within 60 days of Day 0; use of IV or IM	Monitor patients for signs and symptoms of infection, monitor laboratory values, request that patients report signs of infection. Treat infections immediately and appropriately.

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
	placebo were nasopharyngitis, bronchitis, pharyngitis, cystitis, and gastroenteritis viral. Serious infections occurred in 5% of patients receiving either belimumab or placebo.	antibiotics within 60 days of Day 0; a history of or positive test at screening for HIV, hepatatis B or hepatitis C; have Grade 3 or 4 lymphopenia; or have Grade 3 or 4 IgG or IgA deficiency	
Progressive multifocal leukoencephalopathy (PML)	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.		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.	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.
Immunogenecity	As with other monoclonal antibodies, treatment with belimumab could lead to the development of anti-drug antibodies		Monitor anti-drug antibody laboratory values.

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
	(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.		
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 immunisations. 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 immunisations received prior to administration of belimumab.	Exclude patients who have received a live vaccine within 30 days of Day 0.	Do not administer live vaccines concurrently.
Potential	There have been reports of depression	Exclude patients who have	Monitor patients for signs and symptoms of

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
psychiatric events - Depression and suicidality	and suicidality in patients receiving belimumab. 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].	evidence of serious suicide risk including any history of suicidal behaviour 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.	psychiatric events including depression and suicidality, request that patients report signs and symptoms. Treat appropriately

Refer to Section 8.3 for information about the Independent Data Monitoring Committee (IDMC) being used in the study.

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 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. 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).

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.

2. STUDY OBJECTIVES

- To evaluate the efficacy of belimumab in adult SLE subjects of black race.
- To evaluate the safety and tolerability of belimumab in adult SLE subjects of black race.

3. STUDY DESIGN

This is a Phase 3/4, multi-center, international, randomized, double-blind, placebo-controlled, 52-week study to evaluate the efficacy and safety of belimumab in adult black subjects with active SLE. Approximately 501 SLE subjects will be randomized with a target of at least 334 subjects treated with belimumab and 167 subjects receiving placebo.

In addition to receiving stable standard therapy, subjects will be randomized in a 2:1 ratio to treatment with either 10 mg/kg belimumab or placebo. At randomization, subjects will be stratified by their screening SELENA SLEDAI score (8-9 vs $\geq$ 10), complement level (C3 and/or C4 low vs other), and region (US/Canada vs rest of the world). Subjects will be dosed with study agent on Days 0, 14, 28, and then every 28 days through 48 weeks, with a final evaluation at Week 52 (4 weeks after the last dose). Study agent will be administered IV over no less than 1 hour. Subjects will remain under clinical supervision

for 3 hours after completion of the first 2 infusions during the 52-week double-blind phase and 6-month open-label extension.

All subjects will continue the stable standard therapy they were receiving during the screening period. Subjects who complete dosing up to 48 weeks will return for a Day 364/Week 52 (final evaluation) visit. Subjects who successfully complete the initial 52 week double-blind phase may enter into a 6-month open-label extension. The Day 364/Week 52 visit will serve as the Day 0 visit for subjects entering the 6-month open-label extension. Subjects on active drug or placebo will receive belimumab 10 mg/kg IV every 28 days for 6 months in the open-label extension. The 1st dose on the 6-month open-label extension will be given on Day 364 (Week 52) of the double-blind treatment phase following the completion of all Day 364 (Week 52) assessments. Subjects participating in the 6-month open-label extension will continue to be monitored for safety and more latitude will be permitted for background medication changes as outlined in Section 5.5. Subjects who complete the 52-week double-blind phase, but do not enter the 6-month open-label extension will be required to return for an additional follow up visit 8 weeks after the last dose of study agent. Subjects who withdraw early will be required to return for an Exit visit (4 weeks after the last dose of study agent) and a follow-up visit approximately 8 weeks after their last dose of study agent. The 8-week follow up visit is not required for subjects entering the separate continuation protocol. In the event that a subject discontinues study agent at any time during the study or withdraws consent, an attempt will be made to ascertain survival status approximately 52 weeks after the first dose of study agent.

At the end of the 6-month open-label period, subjects who 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 a separate continuation protocol. A separate informed consent will need to be provided for the continuation protocol.

4. INCLUSION AND EXCLUSION CRITERIA

4.1. Inclusion Criteria

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

1. Are at least 18 years of age.
2. Are self-identified black race.
3. Have a clinical diagnosis of SLE according to the American College of Rheumatology (ACR) criteria (see Appendix 1).
4. Have active SLE disease defined as a SELENA SLEDAI score ≥ 8 at screening (refer to Appendix 5 and Section 6.8.1.1 Scoring for Proteinuria for Eligibility at Screening).
5. Have 2 unequivocally positive autoantibody test results defined as a positive antinuclear antibody (ANA) test [ie, titer ≥ 1:80 by HEp-2 immunofluorescence assay (IFA) and/or positive enzyme immunoassay (EIA)] and/or a positive anti-dsDNA (≥ 30 IU/mL) serum antibody test as follows:

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

  OR

- One positive historical test result and 1 positive test result during the screening period.
  Historical documentation of a positive ANA test (eg, HEp-2 IFA or EIA) or anti-dsDNA (eg, anti-dsDNA by any validated commercial assay) must include the date and type of the test, the name of the testing laboratory, numerical reference range, and a key that explains values provided as positive vs negative OR negative, equivocal/borderline positive). Only unequivocally positive values as defined in the laboratory's reference range are acceptable; borderline values will not be accepted.

6. Are on a stable SLE treatment regimen consisting of any of the following medications (alone or in combination) for a period of at least 30 days prior to Day 0 (ie, day of 1st dose of study agent) [Refer to Section 5.5.1 for allowable medications and maximum dose]:
   - Corticosteroids (prednisone or prednisone equivalent, up to 40 mg/day):
     - For subjects on SLE combination therapy, their stable steroid dose must be fixed within the range of 0 to 40 mg/day (prednisone or prednisone equivalent).
     - For subjects whose only SLE treatment is steroids, their stable steroid dose must be fixed within the range of 7.5 to 40 mg/day (prednisone or prednisone equivalent).
     - For those subjects on alternating day doses of steroids, use the average of 2 daily doses to calculate the average daily steroid dose.
   - Other immunosuppressive or immunomodulatory agents including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), calcineurin inhibitors (eg, tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine, mizoribine, or thalidomide.
   - Anti-malarials (eg, hydroxychloroquine, chloroquine, quinacrine).
   - Non-steroidal anti-inflammatory drugs (NSAIDs).

   NOTE:
   - Pre-existing SLE medications must be stable for at least 30 days prior to Day 0.
   - Corticosteroids may be added as new medication or their doses adjusted only up to 30 days prior to Day 0 (see Exclusion Criterion #6).
   - New SLE therapy other than corticosteroids must not be added within 60 days of Day 0 (see Exclusion Criterion #5).
7. A female subject is eligible to enter the study if she is:
   - Not pregnant or nursing;
   - Of non-childbearing potential defined as

- pre-menopausal females with a documented tubal ligation, hysterectomy, documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion, or documented bilateral oophorectomy or
- postmenopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile [eg, > 45 years, in the absence of hormone replacement therapy or other cause for amenorrhea]; in questionable cases obtain a blood sample for follicle stimulating hormone (FSH) and estradiol simultaneously to confirm. Diagnostic levels for FSH and estradiol vary by specific laboratories/assays;

- OR is of child-bearing potential with negative pregnancy test as determined by serum human chorionic gonadotrophin (hCG) test at screening and urine hCG test prior to dosing AND
  - Agrees to use one of the contraception methods listed in the protocol (see Section 4.3) for 2 weeks prior to the day of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until 16 weeks following the last dose of study agent.
- OR has only same-sex partners, when this is her preferred and usual lifestyle.

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. Have received treatment with anti-BLyS [belimumab]) at any time.
2. Have received any of the following within 364 days of Day 0:
   - Abatacept.
   - Other B cell targeted therapy (eg, rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI-Fc, or anti-BAFF (LY2127399).
   - A biologic investigational agent other than B cell targeted therapy (e.g., 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.)
3. Have required 3 or more courses of systemic corticosteroids for concomitant conditions (eg, asthma, atopic dermatitis) within 364 days of Day 0. (Topical or inhaled steroids are permitted.)
4. Have received any of the following within 90 days of Day 0:
   - Anti-TNF therapy (eg, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab).
   - Intravenous (IV) cyclophosphamide

- Interleukin-1 receptor antagonist (anakinra).
- Intravenous immunoglobulin (IVIG).
- High dose prednisone or equivalent (> 100 mg/day).
- Plasmapheresis.

5. Have received any of the following within 60 days of Day 0:
   - A non-biologic investigational agent.
   - Any new immunosuppressive/immunomodulatory agent, anti-malarial, or NSAID (see Inclusion Criterion #6).

   Note: New inhaled and topical steroids and new topical immunosuppressive agents (eg, eye drops, topical creams) are allowed. Any NSAID use for < 1 week is allowed.
   - Any steroid injection (eg, intramuscular, intraarticular, or intravenous).
6. Have received any of the following within 30 days of Day 0:
   - A live vaccine.
   - A change in dose of a corticosteroid, other immunosuppressive/immunomodulatory agent, anti-malarial, or NSAID (see Inclusion Criterion #6).
7. Have severe lupus kidney disease (defined by proteinuria > 6 g/24 hour or equivalent using spot urine protein to creatinine ratio, or serum creatinine > 2.5 mg/dL), or have severe active nephritis requiring acute therapy not permitted by protocol (eg, IV cyclophosphamide within 90 days of Day 0), or have required hemodialysis or high-dose prednisone (> 100 mg/day) within 90 days of Day 0.
8. Have severe active central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident [CVA], cerebritis, or CNS vasculitis) requiring therapeutic intervention within 60 days of Day 0.
9. Have a history of a major organ transplant (eg, heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant.
10. 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.
11. 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.
12. 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.
13. 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 Day 0.

- Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of Day 0.

14. 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 screening Columbia-Suicide Severity Rating Scale (C-SSRS) (refer to Appendix 3 for baseline/screening C-SSRS) in the last 2 months or who, in the investigator's opinion, pose a significant suicide risk.
15. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 0.
16. Have a historically positive test or test positive at screening for HIV antibody, hepatitis B surface antigen (HBsAg), hepatitis B core antibody, or hepatitis C antibody.
17. Have an IgA deficiency (IgA level < 10 mg/dL).
18. Have a Grade 3 or greater laboratory abnormality based on the Adverse Event Severity Grading Tables (Appendix 12) except for the following that are allowed:
    - Stable Grade 3 prothrombin time (PT) secondary to anticoagulant, eg, 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 3/4 proteinuria (≤ 6 g/24 hour equivalent by spot urine protein to creatinine ratio allowed).
    - Stable Grade 3 hypoalbuminemia due to lupus nephritis, and not related to liver disease or malnutrition.
    - 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 ALT and/or AST must be ≤ Grade 2.
    - Stable Grade 3 hemoglobin reduction due to lupus.
    - Stable Grade 3 neutropenia or stable Grade 3 white blood cell count.
19. Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins, or monoclonal antibodies.

4.3. Contraception Requirements for Female Subjects

Female subjects of childbearing potential must not become pregnant during the study and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%. Female subjects of childbearing potential with same sex partners (when this is their preferred and usual lifestyle) are not required to be abstinent or to use contraception.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (eg calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of < 1%

- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of levonorgestrel or etonogestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) with <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository).

NOTE: MMF and other forms of mycophenolate affect the metabolism of oral contraceptives and may reduce their effectiveness. As such, women receiving mycophenolate who are using oral contraceptives for birth control should employ an additional method (eg, barrier method).

NOTE: These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

5. STUDY TREATMENT REGIMEN

5.1. Study Agent Name and Formulation

The common name of the investigational product 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 0.16 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) by the assigned treatment group and the subject's current body weight in kilograms (kg) obtained at each visit prior to dosing. At sites where it is impractical to use the subject's current body weight to calculate the dose, it is permissible for the Week 2 visit onward to use the subject's body weight from the previous visit (eg, the Day 0 weight can be used to calculate the dose for the Week 2 visit). However, the subject's body weight will be measured prior to dosing and if the previous visit weight and current visit weight vary by more than 10%, then the weight measured at the current visit must be used. 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), 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 6.8). 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 consist of one active treatment arm (10 mg/kg belimumab) and a placebo arm, with both treatment groups receiving standard therapy. All study agent treatments will be administered IV over no less than 1 hour. Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days thereafter through 48 weeks of treatment. Subjects who complete the initial treatment period (48 weeks of treatment with final assessment at Week 52) will be given the option to receive belimumab in the 6-month open-label extension phase.

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 reactions, and monitor subjects closely. In the event of a serious reaction, study agent administration must be discontinued immediately and the appropriate medical therapy administered.

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 phase and the 6-month open-label extension. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing any untoward reactions. 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 the study sites' guidelines or standard operating procedure for IV infusions.

Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. For further information, see the belimumab IB.

5.4. Alteration of Dose/Schedule Due to Toxicity

The dose of study agent administered may not be altered. The infusion rate may be slowed or interrupted if the subject appears to develop signs of adverse reaction or infusion-associated symptoms (see Section 5.3). 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 possibly 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 possibly related to study agent, then treatment with study agent will be discontinued. The subject should be withdrawn from the study agent and followed until resolution of the AE(s). The subject must also return for an Exit visit 4 weeks after the last administration of study agent and a follow-up visit 8 weeks after the last administration of study agent. An attempt will be made to ascertain survival status approximately 52 weeks after the first dose of study agent.

5.5. Concurrent Medications

This section reviews the medications and the doses allowed and prohibited during the course of the study. Any time the concurrent medication requirements are not followed, subjects are considered treatment failures (refer to Appendix 2). Subjects who meet a treatment failure criterion prior to completing IP administration at Week 48 should be withdrawn from IP and not permitted to enter the 6-month open-label extension of the protocol. The subject must return for an Exit visit 4 weeks after the last administration of study agent and a follow-up visit 8 weeks after the last administration of study agent. An attempt will be made to ascertain survival status approximately 52 weeks after the first dose of study agent. If a subject completes all IP dosing through Week 48 of the protocol, and at the Week 52 protocol visit it is determined that a subject has met a treatment failure criterion, the subject should complete the Week 52 assessments in the double-blind period, and after consultation with the Medical Monitor, consideration may be given for the subject to enter into the 6-month open-label extension. The subject will still be deemed a treatment failure from the date the criterion was met for analysis purposes.

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

5.5.1. Allowable Medications

Subjects must be on a stable SLE treatment regimen for at least 30 days prior to Day 0 (see Section 4.1 and Section 4.2).

Once the subject is randomized and receives the 1st dose of study agent on Day 0, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically required; however, changes in certain medications (as outlined below) may result in the subject being defined as a treatment failure and may require withdrawal from the study following consultation with the medical monitor (see Section 5.5). Starting a new protocol-prohibited or restricted medication on the day of the Day 364 (Week 52) visit will not be used to classify treatment failure status. A schematic overview of the adjustments permitted is provided in Appendix 2.

During the 6-month open-label phase (from the Week 52 visit in the double-blind treatment period and beyond), the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate. Investigators are encouraged to consider the guidance provided in Section 5.5.1.2 regarding corticosteroid reduction during periods of stable SLE disease. The American College of Rheumatology (ACR) draft guidance regarding steroid dosing and tapering in response to SLE flare is provided in Appendix 6. Prohibited medications as outlined in Section 5.5.2 will still apply.

5.5.1.1. Anti-malarials

- A new anti-malarial (eg, hydroxychloroquine, chloroquine, quinacrine) may be started between Day 0 and the Day 112 (Week 16) visit.
- The dose of an anti-malarial may be reduced during the course of the study. The dose of an anti-malarial may be increased as clinically required, up to the Day 112 (Week 16) visit.
- After the Day 112 (Week 16) visit, any increase in dose of an anti-malarial over the baseline (Day 0) or Day 112 (Week 16) visit dose, whichever is higher, will declare the subject a treatment failure.
- Starting any new anti-malarial treatment after the Day 112 (Week 16) visit will declare the subject a treatment failure.
  - An anti-malarial treatment will be considered new if the subject did not receive an anti-malarial at any time during the Day 0 to Day 112 (Week 16) treatment interval.
- An anti-malarial may be replaced by another anti-malarial due to documented toxicity or lack of availability at any time during the study.

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

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

- Compounded anti-malarials – no individual component may exceed the maximum dose above.

*Clinical loading dose is permitted for initiation or replacement.

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

5.5.1.2. Corticosteroids

In this section, total systemic steroid dose is defined as the average daily dose of all steroids taken SC, IV, IM, intradermally, and orally for both SLE and non-SLE reasons. At baseline, the average daily dose of steroids is the sum of steroid dose over 7 consecutive days up to, but not including Day 0, divided by 7. While on treatment, the average daily dose of steroids is the sum of steroid dose over any 7 consecutive days divided by 7 in the respective time window.

5.5.1.2.1. Systemic Steroids for SLE-related Disease Activity

- The total dose of systemic steroids as defined above may be increased as clinically required during the first 6 months of the trial (ie, until the Day 168 [Week 24] visit), but must return to within 25% or 5 mg over the baseline (Day 0) dose, whichever is higher, by the Day 168 (Week 24) visit.
- A subject who fails to return to within 25% or 5 mg over the baseline (Day 0) dose, whichever is higher, by the Day 168 (Week 24) visit will be considered a treatment failure.
- After the Day 168 (Week 24) visit, an increase > 25% or > 5 mg over the baseline (Day 0) dose, whichever is higher, for SLE activity will deem the subject a treatment failure.
- Within 8 weeks before the Day 364 (Week 52) visit, no new increase over the baseline (Day 0) or Day 308 (Week 44) visit dose, whichever is higher, is allowed. A new increase would deem the subject a treatment failure.

5.5.1.2.2. Intraarticular Injections

- Subjects may receive intraarticular injections between baseline (Day 0) and the Day 308 (Week 44) visit.
- A subject who receives any intraarticular injection(s) within 8 weeks before the Day 364 (Week 52) visit will be defined as a treatment failure for analysis.

5.5.1.2.3. Steroids for Reasons Other Than SLE Disease Activity

From Day 0 to the Day 168 (Week 24) Visit:

Steroids may be given for reasons other than SLE disease activity (such as asthma, contact dermatitis) as clinically indicated until Day 168 (Week 24) visit.

From Days 168 to 308 (Weeks 24 to 44) Visits:

Steroids may be given for reasons other than SLE disease activity from the Day 168 (Week 24) visit until the Day 308 (Week 44) visit at any dose/duration that does not result in a total steroid dose (for SLE and non-SLE reasons) > 25% or > 5 mg, whichever is higher, over the baseline dose. Any total steroid dose exceeding this rule will deem the subject a treatment failure. In addition, steroids for non-SLE reasons may be given short-term at higher doses according to the following guidelines:

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

and/or

- Up to 100 mg/day (prednisone) for 2-3 days ,

and/or

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

The duration of high dose steroids use for reasons other than SLE must not exceed 7 days, after which time, tapering should begin. The total steroid dose must be tapered to within 25% or 5 mg over the baseline dose, whichever is higher, within 30 days of the 1st dose of a course of steroids. In addition, the steroid dose must be tapered to within 25% or 5 mg over the baseline dose, whichever is higher, by the Day 308 (Week 44) visit. Otherwise the subject will be deemed a treatment failure.

From the Day 308 to 364 (Week 44 to 52) Visits:

After the Day 308 (Week 44) visit through the Day 364 (Week 52) visit, no new steroids are allowed for reasons other than SLE activity that result in a total daily steroid dose > 25% or > 5 mg, whichever is higher, over the baseline total steroid dose. A subject will be considered a treatment failure for any steroid use 8 weeks before the Day 364 (Week 52) visit that does not meet this criterion.

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

5.5.1.2.4. Tapering or Restoration/Restart of Steroids

The primary objective of this trial is to evaluate the ability of belimumab to reduce SLE disease activity. Premature or rapid reduction in steroids may confound interpretation of study results and could induce a flare. However, it is understood that an important goal of therapy is to reduce steroids, given their associated morbidity. As such, subjects who have improving SLE disease activity for at least 8 weeks may, at the investigator's discretion, reduce the steroid dose targeting a reduction to 7.5 mg/day or lower after the Day 168 (Week 24) visit. Investigators should consider the guidance provided in Table 5-1 below. This table reflects the ACR draft guidance regarding steroid reduction during periods of stable SLE disease. If the subject continues to have stable or improving disease activity after 4 weeks on a reduced dose, then the investigator may consider reducing the dose again. During attempts to wean subjects from steroid use altogether, alternating

dosages (eg, alternating 6/3/6 mg/day) are permitted to help guard against Addisonian crises. Caution should be exercised when discontinuing steroids before the Day 364/Exit (Week 52) visit, given the potential to induce a flare and thereby confound the study results.

If a subject has had worsening SLE disease activity, then a 12-week period of stable or improving disease activity should be observed before considering a clinically significant steroid dose reduction. (Note: The investigator may always apply their clinical judgment as to whether a dose reduction is appropriate.)

Subjects who have their prednisone or equivalent tapered may have their dose increased up to the maximum allowed as defined in Section 5.5.1.2.1 and Section 5.5.1.2.3 (see Appendix 6).

Table 5-1 Algorithm for reducing dose of prednisone

Daily Dose (mg)	Dose Reduction (mg)
Up to 7.5	1.0
> 7.5 to 15	2.5
> 15 to 30	5.0
> 30 to 40	10.0
> 40	Taper at the investigator's discretion using draft guidelines prepared for ACR (see Appendix 6)

5.5.1.2.5. Treatment of SLE Flares with Steroids

If a subject has an SLE flare requiring an increase in steroid dose before the Day 168 (Week 24) visit, the investigator should consider the draft guidelines prepared for the ACR (ACR Ad Hoc Working Group, 2004) for steroid dose/duration of induction therapy and recommended time for tapering the dose to baseline (Day 0) provided in Table 5-2 below. The subject must return to within 25% or 5 mg over the baseline (Day 0) steroid dose, whichever is higher, on or before the Day 168 (Week 24) visit or they will be considered a treatment failure. If a subject's dose is increased > 25% or > 5 mg over the baseline dose, whichever is higher, any time after the Day 168 (Week 24) visit, they are also considered a treatment failure.

Table 5-2 Recommended, standardized initial steroid dosing and steroid tapering algorithm for treatment of an SLE flare

	Dose[1] Induction (Median)	Range	Mean ± SD	Duration of Induction Therapy (Median)	Duration to Off Steroids (Median)
Severe SLE	60 PO	40-100	66.4 ± 15.5	14 days	20 weeks
	1000 bolus	40-1000	766 ± 344	3 days	-
Moderately Severe SLE	35 PO	15-75	38.5 ± 13.4	7 days	15 weeks
Mild SLE	10 PO	0-30	14.5 ± 6.8	not determined	not determined

[1] Prednisone dose in mg for a 70-kilogram person.

(From: Criteria for Steroid-Sparing Ability of Interventions in Systemic Lupus Erythematosus: Report of a Consensus Meeting; Arthritis & Rheumatism; Nov 2004).

5.5.1.3. Other Immunosuppressive/Immunomodulatory Agents

The primary objective of this trial is to evaluate the ability of belimumab to reduce SLE disease activity. Premature or rapid reduction in immunosuppressant/immunomodulatory agents may confound interpretation of study results and could induce a flare.

- Starting any new immunosuppressive/immunomodulatory agent after Day 0 will cause the subject to be declared a treatment failure.
- The dose of existing immunosuppressive/immunomodulatory agents may be increased, as clinically required, up to the Day 112 (Week 16) visit.
- After the Day 112 (Week 16) visit, any increase in dose over the baseline (Day 0) or Day 112 (Week 16) visit dose, whichever is higher, will cause the subject to be declared a treatment failure.

The allowable maximum doses for immunosuppressives at baseline (Day 0) and during the study are listed below:

- Azathioprine – 300 mg/day.
- 6-mercaptopurine – 300 mg/day.
- Mycophenolate mofetil (PO)/mycophenolate mofetil hydrochloride (IV) – 4 g/day.
- Mycophenolate sodium (PO) – 2.88 g/day.
- Methotrexate – 25 mg/week.
- Oral cyclophosphamide – 2.5 mg/kg/day.
- Cyclosporine – 4 mg/kg/day*.
- Tacrolimus – 0.2 mg/kg/day*.
- Sirolimus – 2 mg/day*.
- Thalidomide – 200 mg/day.
- Leflunomide – 40 mg/day*.
- Mizoribine – 150 mg/day.

An immunosuppressive/immunomodulatory agent may be replaced with 1 of the agents above due to documented toxicity or lack of availability. For other immunosuppressive agents not listed above, the investigator must contact the Medical Monitor for approval.

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

New topical immunosuppressive agents (eg, eye drops, topical creams) are allowed after Day 0.

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

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

- NSAIDs may be given as clinically indicated until the Day 308 (Week 44) visit.
- For subjects who never received an NSAID between the Day 0 and Day 308 (Week 44) visit, starting a new NSAID after the Day 308 (Week 44) visit will declare the subject a treatment failure unless the NSAID is given for < 1 week.
- An NSAID may be replaced with another NSAID due to documented toxicity or lack of availability.
- Daily doses of aspirin up to 1000 mg/day are allowed at any time during the study.
- Daily doses of aspirin above 1000 mg/day may be initiated at any time up to Day 308 (Week 44) visit and may continue through the end of the study.
- For subjects who never received an aspirin regimen at a dose > 1000 mg/day between the Day 0 and Day 308 (Week 44) visit, starting a new aspirin regimen at a dose > 1000 mg/day after the Day 308 (Week 44) visit will declare the subject a treatment failure unless the aspirin is given for < 1 week.

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

5.5.2. Prohibited Medications and Therapies

Subjects who start prohibited medications or therapies 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 an Exit visit 4 weeks after the last administration of study agent and a follow-up visit 8 weeks after the last administration of study agent. In addition, an attempt will be made to ascertain survival status approximately 52 weeks after the first dose of study agent.

The following medications and therapies are prohibited at any time during the study:

- Other investigational agents (biologic or non-biologic). Investigational applies to any drug not approved for sale in the country in which it is being used.
- Co-enrollment into another study of an investigational agent or another study that may interfere with the conduct of this protocol.
- Anti-TNF therapy (eg, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab).
- Other biologics (eg, rituximab, abatacept, interleukin-1 receptor antagonist [anakinra], tocilizumab).
- Intravenous immunoglobulin (IVIG).
- IV cyclophosphamide.
- Plasmapheresis

5.5.3. 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.

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 must sign the PGx informed consent prior to any PGx samples being drawn from the subject.

The FACIT-Fatigue Scale will only be completed by subjects for whom a survey exists in the subject's language.

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

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

Subjects must be on appropriate stable standard therapy before entering the trial (see Inclusion Criteria Section 4.1 and Section 5.5.1). Investigators should consider this carefully before screening subjects that only recently came under their care. A 60-day observation period is suggested if previous SLE disease activity documentation is suboptimal. This period prior to screening allows the principal investigator to observe the subject and make any necessary medication adjustments, especially if a subject has been recently referred to the study site.

The following assessments are required at screening:

- Demographics (including self-identified race).
- Medical history.
- Weight
- Complete physical examination.
- 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 10 – 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).
  - HIV antibody, HBsAg, HB core antibody, and hepatitis C antibody testing.
  - Biological markers (Complement C3, C4).
  - Serum immunoglobulin isotypes (IgG, IgM, IgA).
  - Autoantibodies (ANA and anti-dsDNA).
- Urine sample for:
  - Routine urinalysis.
  - Alcohol and drug screen.
  - Spot urine for macroscopic/microscopic/proteinuria assessments.
- Disease activity scales:
  - SELENA SLEDAI (see Appendix 5; refer to Section 6.8.1 Guidelines for Scoring Proteinuria).
    - Confirm SLE disease is active, defined as SELENA SLEDAI score ≥ 8 at screening.
  - Physician's Global Assessment (PGA) (see Appendix 5).
  - SLE Flare Index (see Appendix 5).
  - BILAG (see Appendix 7).
- Suicidality assessment by using the Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening assessment form (see Appendix 3 and Section 7.5) at screening.
- 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 or Voice Response System (IWRS/IVRS). Subjects will be randomized in a 2:1 ratio to treatment with either 10 mg/kg belimumab or placebo. At randomization, subjects will be stratified

by their screening SELENA SLEDAI score (8-9 vs ≥ 10), complement level (C3 and/or C4 low vs other), and region (US/Canada vs rest of the world).

6.3. Double-Blind Treatment Period

Subjects will be evaluated at the study site during the scheduled study visits outlined in the Study Calendar in Table 6-1. On Day 0, the subject will be randomized and receive the 1st dose of study agent. After the 1st month of therapy, 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) for a total of 48 weeks of treatment. All efforts should be made to retain subjects on schedule, based on the date of their Day 0 dose.

The final efficacy evaluation will occur at Week 52 (ie, the Day 364/Exit visit, approximately 4 weeks after the last dose of study agent).

Time windows are provided for each study visit after Day 0 in Table 6-1 to allow flexibility in site and subject scheduling. All study visits should occur within the visit window of the scheduled study visit (see Table 6-1).

All subjects who withdraw from treatment prior to Week 52 will be followed (eg phone contact) for survival approximately 52 weeks after the first dose of study agent. In the event that a subject withdraws consent, an attempt should be made at the time of consent withdrawal to obtain consent for survival status.

Subjects who complete the double-blind period through Day 364 (Week 52) will be given the option to receive belimumab in the 6-month open-label extension.

- Subjects who complete the 364 day (52-week) double-blind period, but do not enter the open-label extension, will not have study agent administered at Week 52. Assessments should be completed for the Day 364/Week 52 visit, and then the subject should return in 4 weeks for the 8-week Follow-up Visit.
- Subjects who wish to continue in the open-label extension, will have study agent administered at the Day 364 (Week 52/Day 0 of open-label extension) visit after all Day 364 (Week 52) assessments are performed (refer to Table 6-1 below).

This is an on-treatment Study Calendar. Please refer to Section 6.1 for a complete list of assessments required during screening.

Table 6-1 Study calendar- On-treatment evaluations

		52-Week Double-Blind Treatment Period Days 0-364 (Weeks 0-52)														Post-Treatment Follow-up Period			
Study Day	**Screening**	**Day 0 visit**	**Day 14 visit ± 3 days**	**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**	**Day 364/ EXIT (4-wks post dose) [A, J] ± 7 days**	**Post-txt f-up for non-completers ± 7 days**	**8-week Follow-up [B] ± 7 Days**	**Unscheduled Visit [L]**
Study Week			**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**	**4 wks post last dose**		
Written Informed Consent	X																		
Demographics (including race)	X																		
Medical History and complete Physical Exam	X																		
SLE History/diagnosis	X																		
Eligibility Criteria	X																		
Clinical Assessments:																			
Weight[D]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Symptom-driven Physical Exam		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
C-SSRS Baseline/Screening[I]	X																		
C-SSRS Since Last Visit[I]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Record all current medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

Table 6-1 Study calendar- On-treatment evaluations

		52-Week Double-Blind Treatment Period Days 0-364 (Weeks 0-52)														Post-Treatment Follow-up Period			
Study Day	**Screening**	**Day 0 visit**	**Day 14 visit ± 3 days**	**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**	**Day 364/ EXIT (4-wks post dose) [A, J] ± 7 days**	**Post-txt f-up for non-completers ± 7 days**	**8-week Follow-up [B] ± 7 Days**	**Unscheduled Visit [L]**
Study Week			**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**	**4 wks post last dose**		
SLE Disease Activity Scales[K]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			
SLICC/ACR Damage Index		X														X			
FACIT-Fatigue Scale[C]		X		X	X	X			X			X				X			
Survival assessment[N]																	X		
Laboratory Assessments:																			
HIV, Hepatitis B and Hepatitis C serology	X																		
Alcohol and Drug Screen	X																		
Labs: Hematology & Modified Chem 20 (non-fasting)[E]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
PT/PTT[E]	X	X			X				X							X			
Urinalysis	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Spot urine (protein to creatinine ratio)[F]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X
Pregnancy Test[G]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic Sampling[H]		X	X		X				X							X		X	

Table 6-1 Study calendar- On-treatment evaluations

		52-Week Double-Blind Treatment Period Days 0-364 (Weeks 0-52)														Post-Treatment Follow-up Period			
Study Day	**Screening**	**Day 0 visit**	**Day 14 visit ± 3 days**	**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**	**Day 364/ EXIT (4-wks post dose) [A, J] ± 7 days**	**Post-txt f-up for non-completers ± 7 days**	**8-week Follow-up [B] ± 7 Days**	**Unscheduled Visit [L]**
Study Week			**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**	**4 wks post last dose**		
Immunogenicity[M]		X			X				X							X		X	
B cells		X			X				X							X			
Pharmacogenetic Sampling[M]		X																	
BLyS Protein		X																	
ANA	X	X																	
Complement (C3/C4) and anti-dsDNA	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			
Extractable nuclear antigens (ENAs)[O]		X			X				X							X			
Anti-phospholipid antibodies (aCL, lupus anticoagulant, ±beta-2-glycoprotein-1)[O]		X			X				X							X		X	
Serum IgA, IgM, IgG	X	X			X		X		X		X		X			X		X	
IV Administration of Study Agent[P]																			
		X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Table 6-1 Study calendar - On-treatment evaluations (footnotes)

Refer to Section 6.1 for a list of assessments required for screening/eligibility.

A The Exit (Day 364) visit will occur approximately 4 weeks after the last dose of study agent. For subjects completing all 48 weeks of treatment and continuing into the 6-month open-label extension, this visit will also serve as their 1st (ie, Day 0) visit of the 6-month open-label extension (see Table 6-2). For subjects who discontinue study agent prior to Week 48, the Exit (Day 364) visit should be performed 4 weeks after the last administration of study agent and a follow-up visit 8 weeks after the last administration of study agent, and a survival assessment (eg, by phone contact) will take place approximately 52 weeks after the first dose of study agent (see Footnote N).

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 Must be completed by the subject prior to any study-related discussion with the investigator or study coordinator. The FACIT-Fatigue Scale will only be completed by subjects for whom a survey exists in the subject's language.

D Weight should be obtained prior to dosing at each visit to calculate the dose to be administered. At sites where it is impractical to use the subject's current body weight to calculate the dose, it is permissible to use the subject's body weight from the previous visit. However, the subject's body weight will be measured prior to dosing and if the previous visit weight and current visit weight vary by more than 10% then the weight measured at the current visit must be used.

E Refer to Appendix 10 for a listing of laboratory assessments to be completed. PT/PTT will be assessed according to the separate line item for PT/PTT in this table.

F A 24-hour urine may be done if clinically indicated (eg, renal flare).

G Serum pregnancy test required at screening. Results of urine pregnancy test at subsequent visits, if required, must be available prior to dose. See Section 6.1 (Screening Procedures) for definition of those exempted from subsequent pregnancy testing. 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 7.6).

H Pharmacokinetic sampling: Before the start of infusion on Days 0, 56, and 364 (only if continuing into the 6-month open-label extension); 0-4 hours after the end of infusion on Days 14 and 168; at any time during the visit during the 8-week follow-up visit.

I C-SSRS Since Last Visit form (see Appendix 4) will be used at Day 0 and all subsequent visits. The C-SSRS Baseline/Screening form (see Appendix 3) is only used at Screening.

J Study agent is to be administered only if the subject is continuing into the 6-month open-label extension, and this dose will be the 1st dose in the 6-month open-label extension. The dose should not be administered until the completion of all Day 364/Week 52 assessments.

K SLE Disease Activity Scales: SELENA SLEDAI, SLE Flare Index, BILAG, and PGA. Refer to Section 6.8.1 for guidelines for scoring proteinuria for SELENA SLEDAI evaluation.

L Unscheduled Visits: Other assessments may be performed as clinically indicated.

M Pharmacogenetic (PGx) sampling should be drawn at baseline (Day 0); however, the sample can be taken at any time point during the study. Informed consent must be obtained prior to any blood being taken for PGx research. Samples should be drawn prior to dosing.

N Subjects who discontinue study agent treatment at any time during the study will have a survival assessment (eg, by phone contact) approximately 52 weeks after the first dose of study agent. In the event that a subject withdraws consent, an attempt should be made at the time of consent withdrawal to obtain consent for survival status at Week 52.

O Will be measured in all subjects at Day 0 and samples will be collected at the time points specified; however, the assay will be run only on subjects with elevated titers of these antibodies.

P 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.

(concluded)

6.4. 6-Month Open-Label Extension

Subjects who complete the initial 52-week double-blind treatment period may choose to enter into a 6-month open-label extension. The Day 364/Week 52 visit from the 52-week double-blind treatment period will serve as the Day 0 visit for subjects entering the 6-month open-label extension. Subjects on active drug or placebo will receive belimumab 10 mg/kg IV approximately every 28 days for 6 months in the open-label extension. The 1st dose on the 6-month open-label extension will be given on Day 364 (Week 52) of the double-blind treatment period after the completion of Day 364 (Week 52 assessments) (see Table 6-2 for schedule of evaluations). All 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 participating in the open-label extension will continue to be monitored for efficacy and safety as per the study calendar (see Table 6-2).

During the 6-month open-label extension, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate. Investigators are encouraged to consider the guidance provided in Section 5.5.1.2 regarding corticosteroid reduction during periods of stable SLE disease. The American College of Rheumatology (ACR) draft guidance regarding steroid dosing and tapering in response to SLE flare is provided in Appendix 6. The reason for altering any immunosuppressant therapy (eg, toxicity associated with the medication, fluctuations in disease activity, etc) must be recorded in the source documentation. Prohibited medications as outlined in Section 5.5.2 will still apply.

All subjects 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. These visits apply to subjects who have completed as well as those who have withdrawn early from the open-label extension.

After the 6-month open-label extension phase, 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. 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.

Table 6-2 Study calendar 6-month open-label extension

Study Day	Day 0 visit (Week 52/Exit Visit On-Treatment Phase)[a]	Day 28 visit ± 7 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/EXIT (4 weeks post last dose) ± 7 days[b]	8-week Follow-up (8 wks post last dose) + 7 Days[f]
Study Week	**Day 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	
IV administration of study agent[h]	X	X	X	X	X	X	X		
Clinical Assessments:									
Weight[d]	See Day 364/Exit visit in Week 52 Treatment Period	X	X	X	X	X	X		
Symptom-driven Physical Exam									
C-SSRS Since Last Visit									
Assess/Record Adverse Events		X	X	X	X	X	X	X	X
Record all current medications		X	X	X	X	X	X	X	X
SLE Disease Activity Scales							X	X[e]	
SLICC/ACR Damage Index								X	
FACIT-Fatigue Scale[g]								X	
Laboratory Assessments:									
Labs: Hematology & Modified Chem 20 (non-fasting)	See Day 364/Exit visit in Week 52 Treatment Period						X	X[e]	X
PT/PTT							X		
Urinalysis							X	X[e]	X
Spot urine (protein to creatinine ratio)							X	X[e]	
Urine Pregnancy Test[c]		X	X	X	X	X	X	X	X
Pharmacokinetic Sampling									
Immunogenicity[f]							X	X[e]	X
B cells							X	X[e]	
Complement (C3/C4) and anti-dsDNA							X	X[e]	
Extractable nuclear antigens (ENAs)									
Anti-phospholipid antibodies (aCL, lupus anticoagulant, ±beta-2-glycoprotein-1)									
Serum Immunoglobulin IgG, IgA, IgM				X			X	X[e]	

[a] Day 0 of the 6-month open-label extension is the Day 364/Week 52/Exit study visit from the On-Treatment phase of the study (see Table 6-1) and represents the first belimumab administration for those subjects continuing in the 6-month open-label extension.

[b] All subjects, including subjects who have discontinued study agent prior to Day 196, 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.

[c] Urine pregnancy test, as required, with results available prior to dosing. 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 7.6).

[d] The weight at the current visit will be used for calculating the dose. At sites where it is impractical to use the subject's current body weight to calculate the dose, it is permissible to use the subject's body weight from the previous visit. However, the subject's body weight will be measured prior to dosing and if the previous visit weight and current visit weight vary by more than 10%, then the weight measured at the current visit must be used.

[e] Assessment to be performed only if assessment was not done at Day 168/Week 24.

[f] The 8-week follow up visit is not required for subjects entering the separate continuation protocol.

[g] Must be completed by the subject prior to any study-related discussion with the investigator or study coordinator. The FACIT-Fatigue Scale will only be completed by subjects for whom a survey exists in the subject's language.

[h] 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.

6.5. Exit Visit

Subjects who drop out and do not complete the study will 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 52 visit will be performed for the Exit visit. During the 6-month open-label extension, the assessments for the Week 28 visit will be performed for the Exit visit.

Refer to the Study Calendar (Table 6-1 and Table 6-2) for a list of procedures required at this visit.

6.6. 8-Week Follow-up Visit

All subjects, except those entering the separate continuation protocol, must return for a follow-up visit approximately 8 weeks after the last dose of study agent.

Refer to the Study Calendar (Table 6-1 and Table 6-2) for a list of procedures required at this visit.

6.7. 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 SLE symptoms, AE reporting, or follow-up to a previously reported AE.

Refer to the Study Calendar (Table 6-1) for a list of procedures required at these visits. Other assessments as clinically indicated should be performed.

6.8. Laboratory Tests

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

Due to the potential for unblinding, the following lab results will not be provided to study sites after Day 0: aCL (IgM, IgG, IgA isotypes), ENAs (such as anti-Sm, anti-ribonucleoprotein (anti-RNP), anti-Sjögren Syndrome A (anti-SS-A), anti-Sjögren Syndrome B (anti-SS-B), and anti-ribosomal P), serum immunoglobulin isotypes IgM/IgA, and FACS of peripheral lymphocytes.

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; K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease, 2002a; Price et al, 2005). Given this information, spot urinary protein:urinary creatinine ratio will be used for determining proteinuria in this study for both the SELENA SLEDAI and BILAG disease activity indices.

Measurement of creatinine clearance (CrCl)/glomerular filtration rate (GFR) using timed (for example, 24-hour) urine collections is time consuming and error prone and has consistently been shown to be no more, and often less, reliable than serum creatinine based equations for the estimation of GFR (K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease, 2002b). Therefore, GFR estimated by the Cockcroft-Gault formula will be used in the BILAG disease activity index, as was done in the Phase 2 and Phase 3 trials of belimumab.

Cockcroft-Gault Equation (Cockcroft, 1976)

$$Cl_{cr}\ (mL/min) = \frac{(140\text{-age (yrs)}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad \times 0.85 \text{ if female}$$

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

6.8.1. Guidelines for Scoring Proteinuria for SELENA SLEDAI

The following guidelines should be followed for scoring for proteinuria in the SELENA SLEDAI disease activity index.

6.8.1.1. Scoring for Proteinuria for Eligibility at Screening

In order to be assigned 4 points for proteinuria at screening, the screening spot urine proteinuria assessment must show:

- Proteinuria > 1 g/24 hour equivalent (irrespective of previous value).

OR

- New onset or recurrent proteinuria > 0.5 g/24 hour equivalent or a > 0.5 g/24 hour equivalent increase above the previously documented 24-hour proteinuria or equivalent value obtained within 26 weeks of the screening value. If the screening value is ≤ 1 g/24 hour equivalent and there are no previous assessments of 24-hour proteinuria or spot urinary protein to urinary creatinine ratio available within 26 weeks for a given subject, 4 points cannot be given for proteinuria on the SELENA SLEDAI index, unless a 2nd assessment is done during the screening period of the study (ie, before Day 0).

6.8.1.2. Scoring for Proteinuria at Day 0 and Subsequent Study Visits

According to the SELENA SLEDAI scoring rules, unless the proteinuria continues to rise such that it has increased by > 0.5 g/24 hour equivalent at Day 0 (ie, baseline), the subject, by default, will have an improving SELENA SLEDAI score prior to treatment. Two assessments of 24-hour proteinuria (by spot urinary protein to urinary creatinine ratio) obtained in a 2 to 3 week period are unlikely to show a > 0.5 g/24 hour equivalent increase except in acute renal flare. This is problematic for data analysis since the percent change in the disease activity scales are calculated from the baseline (not screening) SELENA SLEDAI score. As such, the following scoring rules will be applied:

6.8.1.2.1. Scoring for a Subject with Proteinuria and 4 Points Assigned in SELENA SLEDAI

If there is an increase from the last visit of > 0.5 g/24 hour equivalent, only 4 points for proteinuria will continue to be applied (so no subject can get more than 4 points for proteinuria at any 1 time point).

If the proteinuria has not improved (ie, there has not been a decrease in proteinuria of > 0.5 g/24 hour equivalent) since the previous assessment, then 4 points will continue to be assigned on the SELENA SLEDAI index at the current visit.

If proteinuria has improved (decrease of > 0.5 g/24 hour equivalent or a decrease to ≤ 0.5 g/24 hour equivalent) from the previous visit to the current visit, then 0 points will be assigned on the SELENA SLEDAI index at the current visit.

6.8.1.2.2. Scoring for a Subject with 0 Points for Proteinuria in SELENA SLEDAI

If the proteinuria score for SELENA SLEDAI is 0 and at the subsequent visit the assessment of 24-hour proteinuria (by spot urinary protein to urinary creatinine ratio) shows > 0.5 g/24 hour equivalent increase above the previous value or the subject develops new onset of proteinuria > 0.5 g/24 hour equivalent, 4 points will be assigned at this current visit.

6.8.2. Pharmacokinetics

All randomized subjects will be sampled for serum belimumab levels during the double-blind treatment period. A blood sample for pharmacokinetic analysis will be drawn according to the time schedule below.

Table 6-3 PK visit days and sample times

Day (Week)	Time (Related to Dosing of Study Agent)
0	Before the start of infusion
14 (Week 2)	0 - 4 hours after the end of infusion
56 (Week 8)	Before the start of infusion
168 (Week 24)	0 - 4 hours after the end of infusion
364/Exit (Week 52)	Any time during visit (or prior to dosing if going into the open-label extension)
8-week follow-up (8 weeks after last dose)	Any time during visit (if not going into the 6-month open-label extension)

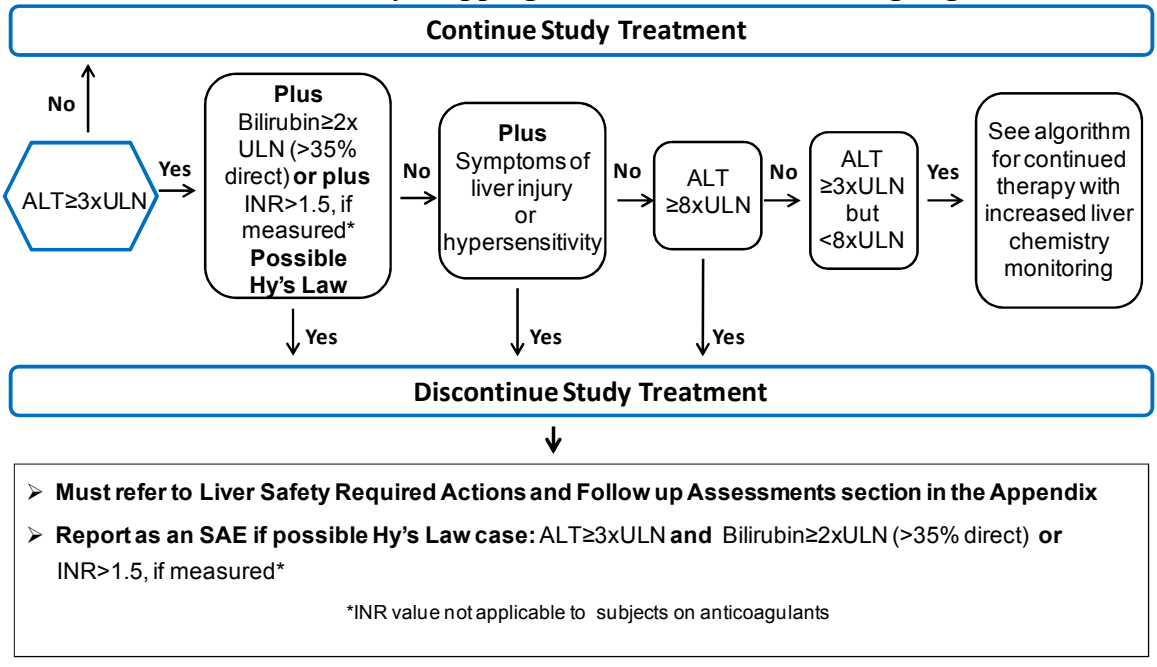
Detailed instructions regarding the collection, processing, storage and shipment of blood samples are available in the Study Procedures Manual that is provided to all study sites.

6.8.3. Liver Stopping 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).

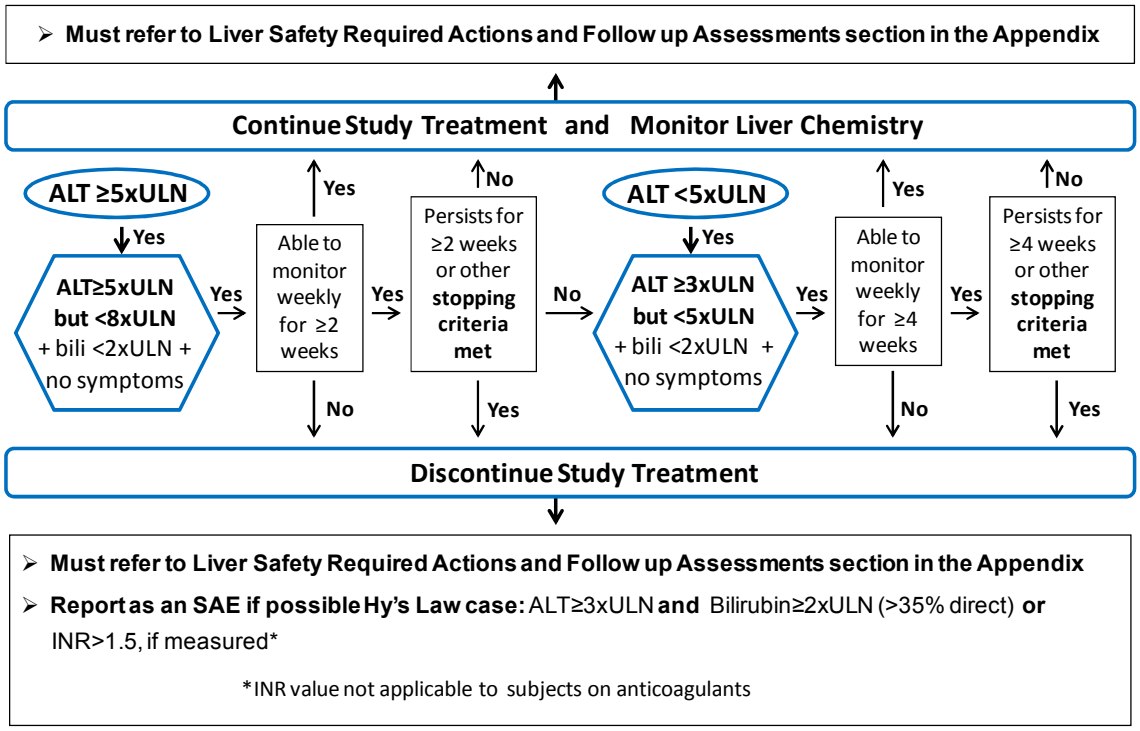
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 13.

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



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 13.

6.8.3.1. Study Agent Restart

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

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

Refer to Appendix 14 for full guidance

6.8.4. Immunogenicity

Serum samples for anti-belimumab antibody measurements will be obtained from all randomized subjects before administration of study agent on Days 0, 56 (Week 8), 168 (Week 24), 364 (Week 52), and at the 8-week follow-up visit (if applicable).

6.9. 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 the study after receiving at least 1 dose of study agent will not be replaced.

Subjects should be withdrawn for any of the following reasons:

- Missing 3 or more consecutive doses of study agent.
- Prohibited concurrent medication or therapy or prohibited dose of concurrent medication or therapy resulting in treatment failure (see Section 5.5).
- Unacceptable toxicity (See Section 5.4 and Section 6.8.3).
- Withdrawal of consent (including use and disclosure of research-related health information).
- Pregnancy.
- Prior to the administration of live vaccine
- At the discretion of the Sponsor, conditions that may warrant termination of a subject include but are not limited to safety concerns, subject significant non-compliance with protocol visits and procedures.

Subjects who discontinue treatment 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. An attempt will be made to contact all discontinued subjects to determine survival status (eg, by phone contact) approximately 52 weeks after the first dose of study agent.

6.10. 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 other 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. 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 other 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 (ie, 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 (eg, 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

   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 hospitalization or prolongation of existing hospitalization

   In general, hospitalization 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 hospitalization are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in disability/incapacity, or

   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 (eg, 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 hospitalization but may jeopardize 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 hospitalization, 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.

Serious Adverse Events (SAEs) must be recorded on the SAE eCRF within 24 hours of site personnel becoming aware of a 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 follow-up information as described in the Study Procedure 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.

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 possibly related to study agent must be reported to the Sponsor as outlined in the Study Procedures Manual.

7.3. Laboratory Abnormalities as Adverse Events

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, 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).

Laboratory tests are graded according to the Adverse Event Severity Grading Tables in Appendix 12. If a particular lab test is not listed in the Appendix, the lab test should be graded mild, moderate, or severe as specified in Section 7.7.

7.4. 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.

7.5. Suicidality Assessment

Some autoimmune diseases have an increased risk of suicidal behavior and/or ideation (Bachen et al, 2009; Stenager et al, 1992; Timonen et al, 2003). In order to objectively assess suicidality in belimumab clinical programs the C-SSRS (Appendix 3 and Appendix 4) 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 this study will be assessed for suicidality at every visit during the double-blind portion of the study.

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 questions 3, 4 or 5 on the C-SSRS prompts the completion of a 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 double-blinded portion of this study using C-SSRS (refer to Appendix 3 and Appendix 4 for C-SSRS). The C-SSRS is a brief measure which is designed to assess

severity and change of suicidality by integrating both behavior 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 this study.

Although assessment of suicidality using the C-SSRS will take place only during the double-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.

7.5.1. 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 behavior 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 behavior 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.

7.6. Reporting a Pregnancy

Any pregnancy that occurs during study participation and up to 16 weeks post dose must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to the Sponsor within 2 weeks of learning of its occurrence. The pregnancy must be followed to delivery to determine outcome (including premature termination) and status of mother and child. To gain additional information on pregnancy outcomes, the subject will be requested to complete a 1 year infant questionnaire.

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.

7.7. 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 12) 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 (ie, 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 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.

7.8. Follow-Up of Adverse Events

Serious and nonserious 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.

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.

7.9. Disease Related Events

Disease related events (DREs) can occur in the study population regardless of belimumab exposure and are not reported as AEs or SAEs, unless judged by the investigator to be more severe than expected for the subject's condition.

The following 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

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, investigators, or IRBs/IECs (unless considered by the Sponsor to be related to study agent).

7.10. 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 (eg, 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 ITT population defined as all subjects who are randomized and received 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 the data through the Day 364 (Week 52) visit for all subjects have been collected, verified, and validated. All subjects and study site personnel will remain blinded until the final database lock and the primary efficacy results become public.

All statistical tests will be 2-sided and performed at an overall significance level of 0.05.

8.2. Randomization Procedure and Assignment to Treatment Groups

This is a Phase 3/4, multi-center, 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 Day 0 visit to be randomly assigned (via an interactive voice or web response system [IVRS/IWRS]) to 1 of 2 treatment groups (belimumab or placebo control) in a 2:1 ratio. The randomization will be stratified by screening SELENA SLEDAI score (8-9 vs $\geq$ 10), complement level (C3 and/or C4 low vs other), and region (US/Canada vs rest of the world).

8.3. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will review unblinded safety data for this Phase 3/4 study on an ongoing basis until the data are locked and analyzed through Week 52. The IDMC will include at least 3 physicians, and a statistician, none of whom are affiliated with the sponsor. 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. The 1st IDMC data review meeting will occur after the first 100 subjects have been treated through Day 56, or within 6 months of the treatment of the 1st subject, whichever is earlier. After the initial review, the committee will review the data approximately every 6 months. At all times the sites and sponsor will remain blinded to treatment allocation. 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 monthly to the IDMC.

After Week 52, the monitoring may be assumed by an internal GSK/HGS committee.

8.4. Sample Size Rationale

Approximately 501 subjects will be randomized and treated in the study, with a target of at least 334 subjects in the arm receiving belimumab and 167 subjects in the arm receiving placebo. This sample size provides at least 90% power at a 5% level of significance to detect a minimum of a 15.55% absolute improvement in the SRI response rate with the modified SLEDAI-2K scoring for proteinuria for the 10 mg/kg belimumab group relative to the placebo group (assumed rate =43.95%) at Week 52. This sample size is also sufficient to provide approximately 80% power at a 5% level of significance to detect a minimum of a 13.4% absolute improvement in the SRI response rate with the SELENA SLEDAI scoring for proteinuria for the 10 mg/kg belimumab group relative to the placebo group (assumed rate = 44.8%).

The selection of the assumed treatment differences is based on the observed SRI data from studies BEL112341 (HGS1006-C1115/BLISS SC) and BEL113750 (Northeast Asia), which are two efficacy studies that concluded in 2015 and 2016, respectively, and have nearly identical eligibility criteria to study HGS1006-C1112 including requiring a screening SS score ≥8. SRI results, calculated using the SS results and calculated using a modification to the proteinuria scoring based on SLEDAI-2K rules, are shown in Table 8-1.

Table 8-1 SRI Results From Studies BEL112341 and BEL113750

	SRI ***Calculated Using the SS Results as Collected***			**SRI** ***Calculated Using SS Results with the Modified SLEDAI-2K Proteinuria Scoring***		
Dataset	**Placebo**	**Belimumab**	**Δ**	**Placebo**	**Belimumab**	**Δ**
BEL112341*	48.4%	61.4%	12.98%	46.6%	61.7%	15.14%
BEL113750**	40.1%	54.3%	14.17%	40.2%	56.3%	16.16%
Pooled BEL112341 and BEL113750	44.8% (222/496)	58.2% (582/1000)	13.44%	43.95% (218/496)	59.50% (595/1000)	15.55%

* Inclusion criterion SS≥8, 200 mg SC dose used.
**Inclusion criterion SS≥8, 10 mg/kg IV dose used.

All sample size calculations were performed using Power Analysis and Sample Size software (PASS 2012).

8.5. Efficacy

8.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the systemic lupus erythematosus responder index (SRI) response rate with the modified SLEDAI-2K scoring for proteinuria at Week 52.

A SRI response is defined as:

- ≥ 4 point reduction from baseline in SELENA SLEDAI score (with the modified SLEDAI-2K scoring for proteinuria),

  AND

- No worsening (increase of < 0.30 points from baseline) in Physician's Global Assessment (PGA),

  AND

- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (ie, at Week 52).

8.5.2. Primary Efficacy Analysis

The proportion of subjects achieving a treatment response at Week 52 will be compared between the belimumab treatment group and placebo using a logistic regression model. The independent variables in the model will include treatment groups (ie, belimumab vs placebo), baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), baseline complement level (C3 and/or C4 low vs other), and region (US/Canada vs rest of the world). However, the adjustment will not occur for any of these baseline randomization factors that has < 10 responders or < 10 non-responders in a stratification level (Peduzzi et al, 1996). The analysis will be performed on the intention-to-treat (ITT) population, defined as all subjects who are randomized and treated with 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.

Any subject who withdraws from the study prior to the Day 364 (Week 52) visit, misses the Day 364 (Week 52) visit (± 28 day window allowed), and/or starts a prohibited medication or dose (see Section 5.5.2) prior to the Day 364 (Week 52) visit will be considered a nonresponder for the Week 52 primary efficacy analysis.

8.5.2.1. Subgroup Analysis

Subgroup analysis, of SRI only, will be performed in the following subgroups:

- Baseline SELENA SLEDAI score (≤ 9 vs ≥ 10).
- Baseline anti-dsDNA (≥ 30 IU/mL vs < 30 IU/mL).
- Baseline prednisone dose level (≤ 7.5 mg/day vs > 7.5 mg/day).
- Baseline complement levels (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)*.
- Region (US/Canada vs other).

A multivariate analysis will also be performed to evaluate how response to belimumab relative to placebo varied across different categories within relevant baseline demographic or disease characteristics. The details will be described in the analysis plan.

*Additional efficacy endpoint analyses in this subgroup will be performed and will be described in the analytical plan.

8.5.3. Secondary Efficacy Endpoints

The major secondary efficacy endpoints include:

1. SRI response rate with the SELENA SLEDAI for scoring of proteinuria at Week 52.
2. Time to first severe flare (as measured by the modified SLE Flare Index; with SLEDAI-2K and SELENA SLEDAI as the SLEDAI criterion of the SFI).
3. Percent of subjects whose average prednisone dose has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52, in subjects receiving greater than 7.5 mg/day at baseline.

8.5.4. Other Efficacy Endpoints

Endpoints Supporting Primary Efficacy Endpoint (SRI where SELENA SLEDAI score is modified to use the SLEDAI-2K scoring for proteinuria):

1. SRI by visit.
2. Percent of subjects with a ≥ 4 point reduction from baseline in SELENA SLEDAI (modified to use the SLEDAI-2K scoring for proteinuria) at Week 52 and by visit.
3. Percent of subjects with no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at Week 52 and by visit.
4. Percent of subjects without PGA worsening (increase of < 0.30 points from baseline) at Week 52 and by visit.
5. Percent of subjects with durable SRI from Week 44-52.
6. Time to the 1st SRI that is maintained through Week 52.
7. Duration of longest response among subjects with at least 1 SRI response.
8. SRI 5-8 at Week 52 and by visit.

The SRI 5-8 are defined identically to the SRI except for using higher thresholds of improvement for SELENA SLEDAI (modified to use the SLEDAI-2K scoring for proteinuria) reduction for a patient to be declared a responder (eg, SELENA SLEDAI ≥ 5 point reduction for SRI5).

Disease activity:

1. Mean percent change and mean change in PGA by visit.
2. Mean percent change and mean change in SELENA SLEDAI with the modified SLEDAI-2K scoring for proteinuria score by visit.

Organ Specific:

1. Percent of subjects with organ improvement by SELENA SLEDAI by visit. The renal domain will use the SLEDAI-2K proteinuria scoring as the primary method with the SELENA SLEDAI proteinuria scoring as a sensitivity analysis.
2. Percent of subjects with organ worsening by SELENA SLEDAI by visit. The renal domain will use the SLEDAI-2K proteinuria scoring as the primary method with the SELENA SLEDAI proteinuria scoring as a sensitivity analysis.
3. Percent of subjects with organ improvement by BILAG by visit.
4. Percent of subjects with organ worsening by BILAG by visit.
5. Mean/median percent (in patients with proteinuria at baseline) and mean/median absolute (in all patients) change in proteinuria by visit.
6. Time to renal flare over 52 weeks (see definition below).
7. Percent of patients developing at least 1 renal flare (see definition below) over 52 weeks.
8. Percent of subjects with doubling of serum creatinine (the proportion of patients whose serum creatinine attains a level double that of the baseline value and is confirmed with a second measurement at least 3 weeks later).

SFI Flare (SFI where SELENA SLEDAI score is modified to use the SLEDAI-2K scoring for proteinuria):

1. Time to flare over 52 weeks.
2. Time to flare after Week 24.
3. Time to severe flare after Week 24.
4. Rate of flare per 100 subject years.
5. Rate of severe flare per 100 subject years.

Steroids (based on average steroid dose between visits):

1. Percent of subjects with daily prednisone dose reduced to ≤ 7.5 mg/day from > 7.5 mg/day at baseline by visit (DO=F).
2. Percent of subjects with daily prednisone dose increased to > 7.5 mg/day from ≤ 7.5 mg/day at baseline by visit (LOCF).
3. Percent of subjects with any increase in steroid use by visit (all patients, LOCF).

4. Percent of subjects with a 50% decrease in steroid dose by visit (DO=F; in patients receiving steroids at baseline).
5. Percent of subjects with a 50% increase in steroid dose by a minimum ≥ 5 mg/day by visit (LOCF; in all patients).
6. Mean/median changes in steroid dose (mg/day) by visit.

SLICC Damage Index (DI):

1. Mean change from baseline in SLICC DI at Week 52.
2. Percent of patients with any SLICC DI worsening (change > 0) at Week 52 compared with baseline.

Patient Reported Outcome:

1. Mean change in FACIT-fatigue score at Week 52 and by visit.
2. Percent of patients with improvement in FACIT-fatigue score exceeding the MCID (≥ 4) by visit.

Biological Markers:

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, anti-phospholipid antibodies [aCL, lupus anticoagulant, ±beta-2-glycoprotein-1], and extractable nuclear antigens [ENAs]).
    - Complement (C3, C4) levels.
3. Percent of patients with normalized serological activity at Week 52 and by visit
    - IgG, IgM and IgA (high to normal/low).
    - Autoantibodies* (anti-dsDNA, ANA, anti-phospholipid antibodies [aCL, lupus anticoagulant, ±beta-2-glycoprotein-1], and extractable nuclear antigens [ENAs]) present to absent.
    - Complement (C3, C4, and C3 AND C4) levels low to normal/high.

*Anti-dsDNA will be collected monthly throughout the study for SELENA SLEDAI scoring modified to use the SLEDAI-2K scoring for proteinuria. ANA will be collected at screening and baseline only. Other autoantibodies will be collected from all patients at baseline, then at regular intervals in patients positive at baseline.

Renal Flare Definition:

The following is the definition of *renal flare* (Alarcón-Segovia et al, 2003) consisting of the development of one or more of the following 3 factors:

- Increased Proteinuria (using spot urine)
  A reproducible increase in 24-hour urine protein levels to:

  > 1,000 mg if the baseline value was < 200 mg

  OR

  > 2,000 mg if the baseline value was between 200 and 1000 mg

  OR

  More than twice the value at baseline if the baseline value was > 1000 mg

- Impaired Renal Function
  A reproducible decrease in GFR of > 20%, accompanied by proteinuria (> 1000 mg/24 hours), hematuria (≥ 4 RBCs/hpf or above the reference range for the laboratory), and/or cellular (RBC and WBC) casts.

- New Hematuria
  New, reproducible hematuria (≥ 11 to 20 RBCs/hpf) or a reproducible increase in hematuria by 2 grades compared with baseline, associated with > 25% dysmorphic RBCs, glomerular in origin, exclusive of menses, accompanied by either an 800 mg increase in 24-hour urinary protein levels or new RBC casts.

8.5.5. Secondary Efficacy Analyses

The SRI response rate with the SELENA SLEDAI scoring for proteinuria at Week 52 will be compared between the belimumab treatment group and the placebo group using the same analysis methods as described for the primary endpoint in Section 8.5.2.

The time to the 1st severe SLE flare over 52 weeks will be compared between the belimumab treatment group and the placebo group using the Cox proportional hazard model. The independent variables in the model will include treatment groups (ie, belimumab vs placebo), baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), complement level (C3 and/or C4 low vs other), and region (US/Canada vs rest of the world). However, the adjustment will not occur for any of these baseline randomization factors that has < 10 events (ie, severe flares) or < 10 non-events in a stratification level. If a subject withdraws from the study or completes the study up to the Day 364 (Week 52) visit without any severe SLE flare, time to the 1st severe SLE flare will be censored at the time of the last observation. If a subject receives a dose of protocol prohibited/restricted medication that results in treatment failure designation up to the Week 52 visit, the subject will be considered as having a severe SLE flare at the time the medication is started.

The percent of subjects with average prednisone dose that has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52 will be compared between the belimumab treatment and the placebo groups using a logistic regression model. The independent variables in the model will include treatment groups (ie, belimumab vs placebo), baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), complement level (C3 and/or C4 low vs other), and region (US/Canada vs rest of the world). However, the adjustment

will not occur for any of these baseline randomization factors that has < 10 events (ie, having a prednisone reduction by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52) or < 10 non-events in a stratification level. The analysis will be performed on subjects who used prednisone > 7.5 mg/day at baseline. Any subject who withdraws from the study prior to the Day 364 (Week 52) visit, misses the Day 364 (Week 52) visit, and/or receives a dose of protocol prohibited/restricted medication that results in treatment failure designation prior to the Day 364 (Week 52) visit will be considered as without any prednisone reduction for the analysis.

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 12) or the grades in Section 7.7, 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 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 3 and Appendix 4)

- Infusion/hypersensitivity reactions
- 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 Table 6-1.

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, preferably on Day 0, but samples may be drawn at any time while the subject is participating in the study, to better characterize genetic variability (eg, HLA typing) that may affect efficacy or safety endpoints. Information regarding PGx research is included in Appendix 11.

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 11). 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 GlaxoSmith Kline 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 eCRFs 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 disk containing the eCRFs for each of their subjects.

10.6. Study Monitoring

The study sponsor, Human Genome Sciences, Inc., or designee, will monitor the study. Study monitors representing the sponsor will visit study sites routinely throughout the trial. The sponsor will review CRFs 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 CRFs 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, the designated unblinded 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 HGS 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 investigator 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 HGS, 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 HGS 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 HGS 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 HGS, 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, 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. Nonerosive 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).

Criterion*	Definition
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 Concurrent Medications

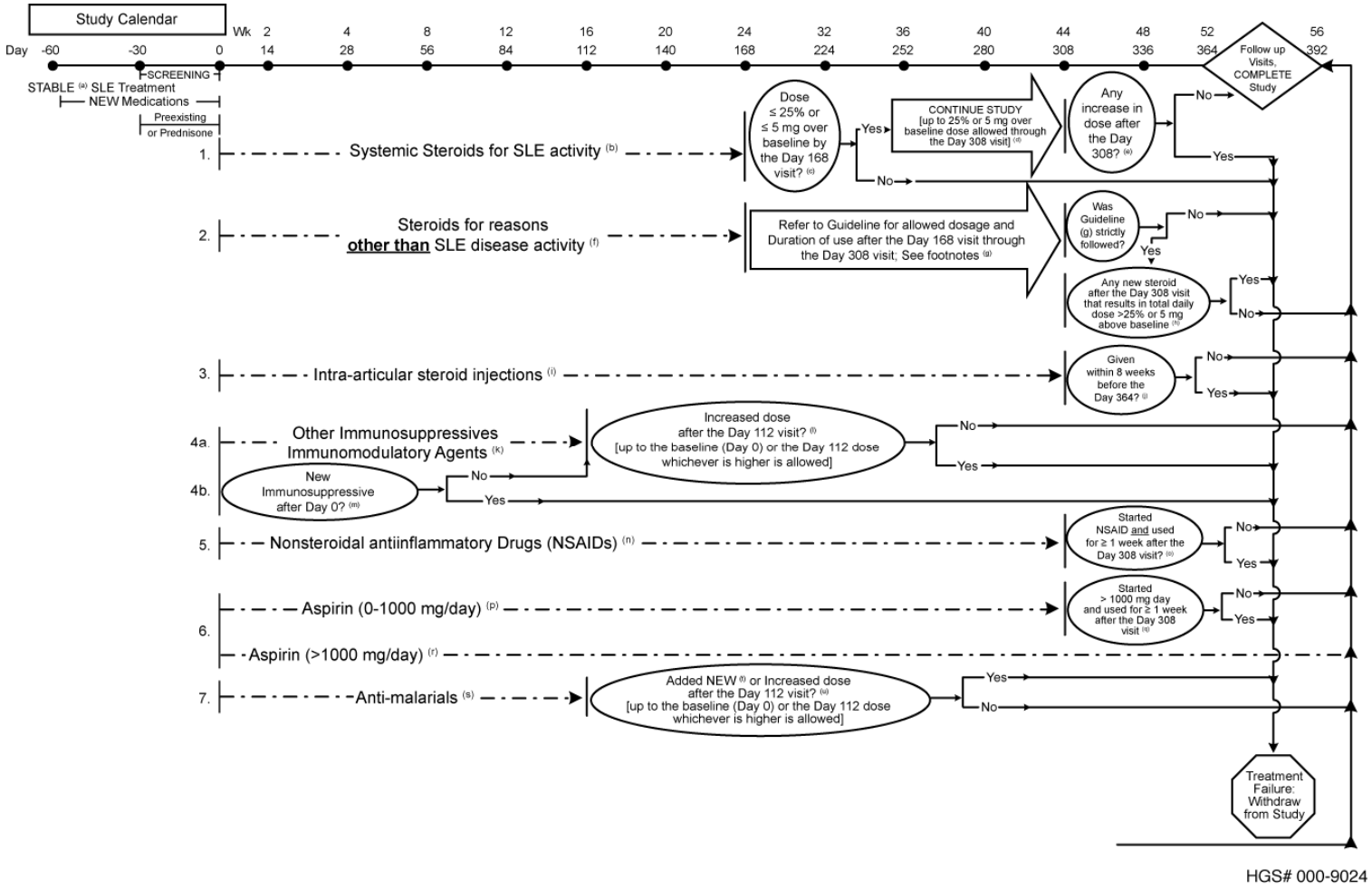


Figure 2-1 Concurrent Medications

Key to Figure 2-1:

Once the subject is randomized and receives the 1st dose of study agent on Day 0, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically required; however, changes in certain medications (as outlined below) may result in the subject being defined as a treatment failure and will require withdrawal from the study.

If background medications are adjusted that may affect entry criteria, a subject may need to be re-screened in order to ensure at least 30 days of stable therapy.

a. Stable SLE treatment regimen may consist any of the following (alone or in combination) for a period of at least 30 days prior to Day 0:
   - Steroids (prednisone or prednisone equivalent, up to 40 mg/day).
   - Anti-malarials (eg, hydroxychloroquine, chloroquine, quinacrine).
   - Non-steroidal anti-inflammatory drugs (NSAIDs).
   - Other immunosuppressive or immunomodulatory agents (eg, methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), calcineurin inhibitors (eg, tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine, mizoribine, thalidomide).
     Pre-existing SLE medications must be stable for at least 30 days prior to Day 0.

     New SLE therapy other than corticosteroids must not be added within 60 days of Day 0. Corticosteroids may be added as new medication or their doses adjusted only up to 30 days prior to Day 0.

b. The total dose of systemic steroids may be increased as clinically required during the first 6 months of the trial (ie, until the Day 168 [Week 24] visit), but must return to within 25% or 5 mg over the baseline (Day 0) dose, whichever is higher, by the Day 168 (Week 24) visit.
c. A subject who fails to return to within 25% or 5 mg over the baseline (Day 0) dose of systemic steroids, whichever is higher, by the Day 168 (Week 24) visit will be considered a treatment failure.
d. After the Day 168 (Week 24) visit, an increase > 25% or > 5 mg over the baseline (Day 0) dose(s) of systemic steroids, whichever is higher, for SLE activity will deem the subject a treatment failure.
e. Within 8 weeks before the Day 364 (Week 52) visit, no new increase of the systemic steroids over the baseline (Day 0) or Day 308 (Week 44) visit dose, whichever is higher, is allowed.
f. Steroids may be given for reasons other than SLE disease activity (such as asthma, contact dermatitis) as clinically indicated until the Day 168 (Week 24) visit.
g. GUIDELINE for Use of Steroids for reasons other than SLE:

From Day 168 to 308 (Week 24 to 44) Visits:

Steroids may be given for reasons other than SLE disease activity from the Day 168 (Week 24) visit until the Day 308 (Week 44) visit at any dose/duration that does not result in a total steroid dose (for SLE and non-SLE reasons) > 25% or > 5 mg, whichever is higher, over the baseline dose. In addition, steroids for non-SLE reasons may be given short-term at higher doses according to the following guidelines:

- Up to 750 mg (prednisone) for 1 day; and/or
- Up to 100 mg/day (prednisone) for 2-3 days; and/or
- Up to 40 mg/day (prednisone) for 4-7 days.

The duration of high dose steroids use for reasons other than SLE must not exceed 7 days, after which time, tapering should begin. The total steroid dose must be tapered to within 25% or 5 mg over the baseline dose, whichever is higher, within 30 days of the 1st dose of a course of steroids. In addition, the steroid dose must be tapered to within 25% or 5 mg over the baseline dose, whichever is higher, by the Day 308 (Week 44) visit.

h. From the Day 308 to 364 (Week 44 to 52) Visits:

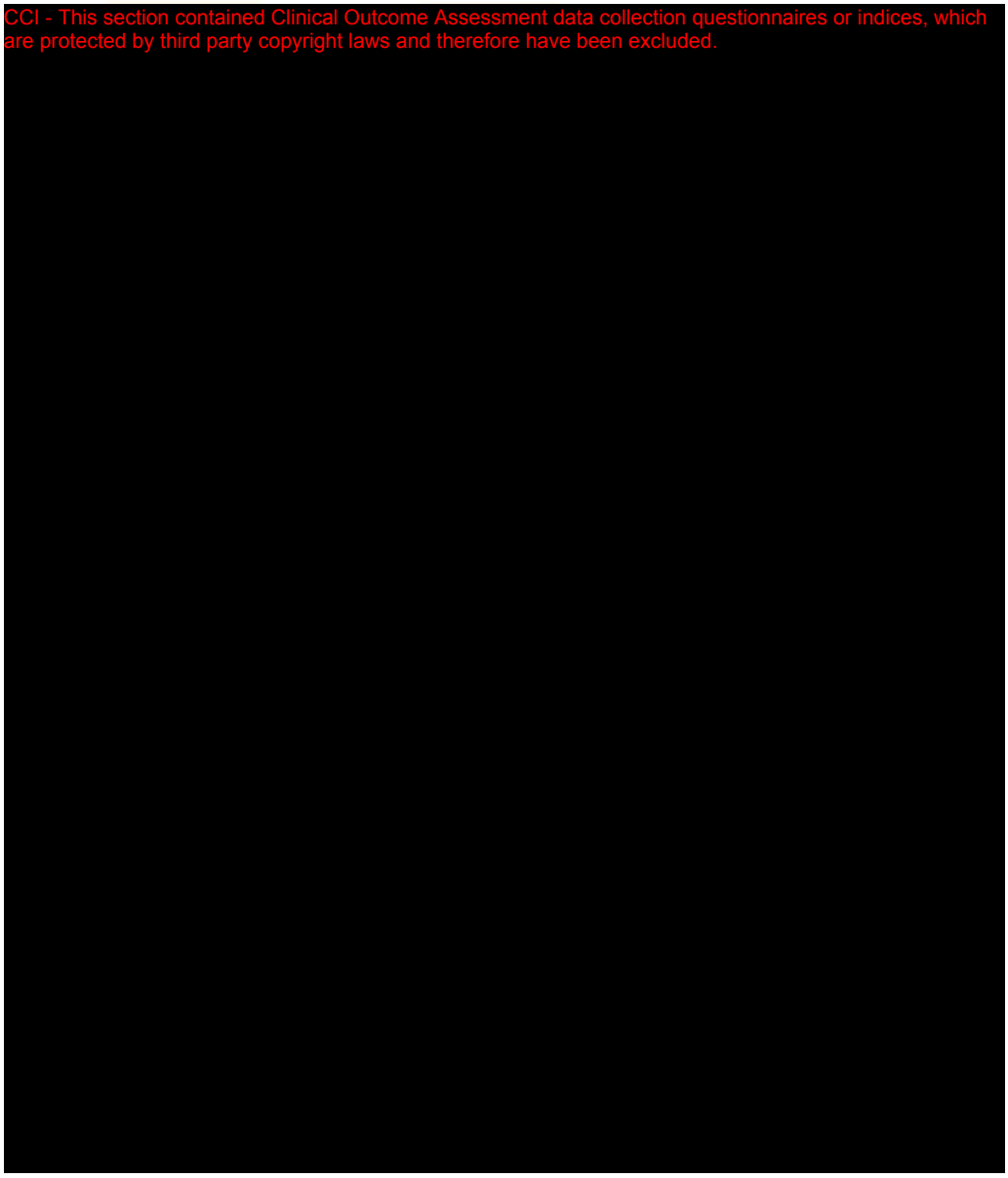
After the Day 308 (Week 44) visit, no new steroids are allowed for reasons other than SLE activity that result in a total daily steroid dose > 25% or > 5 mg, whichever is higher, over the baseline total steroid dose. A subject will be considered a treatment failure for any steroid use 8 weeks before the Day 364 (Week 52) visit that does not meet this criterion.

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

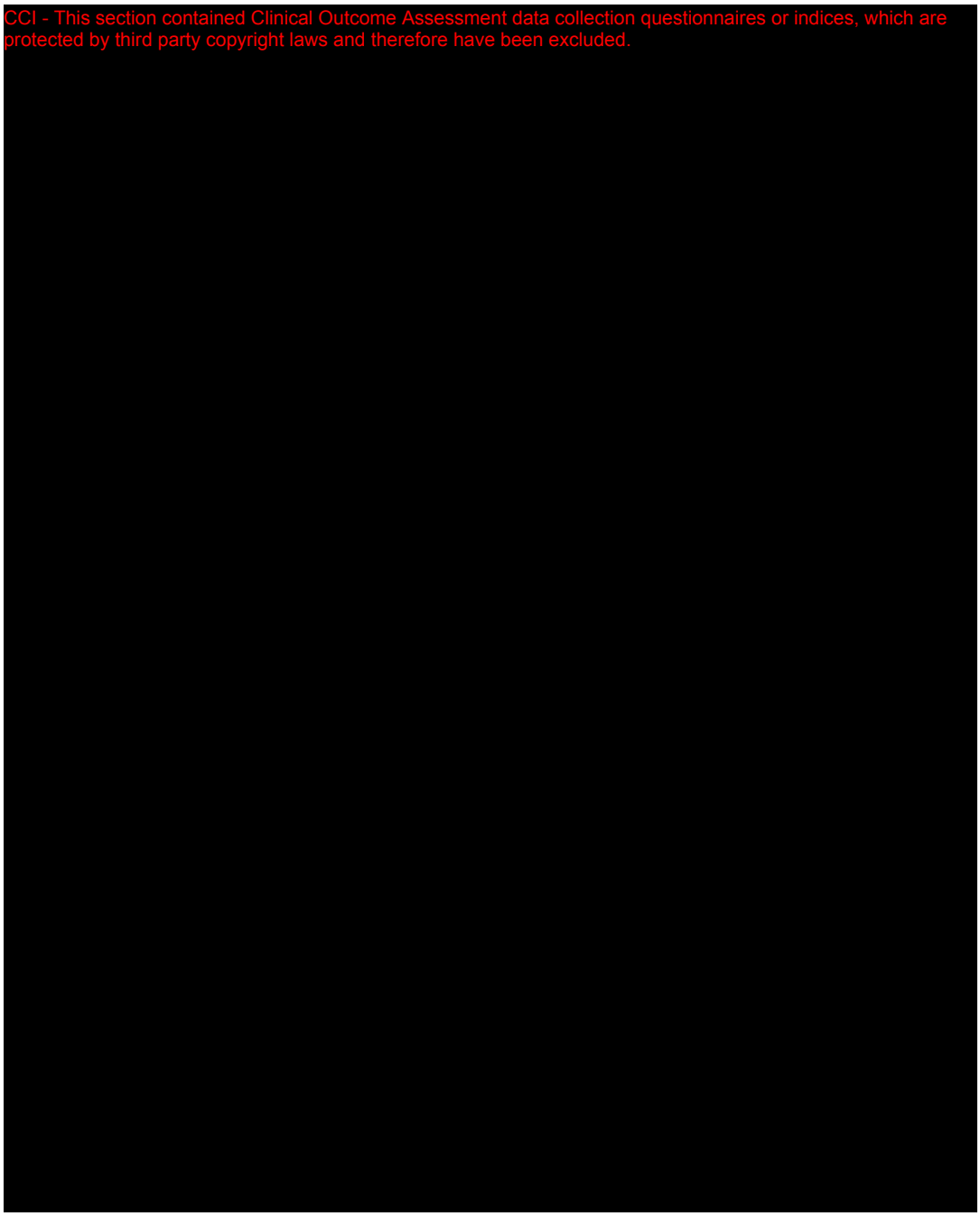
i. Subjects may receive intraarticular steroid injections between baseline (Day 0) and the Day 308 (Week 44) visit.
j. A subject who receives any intraarticular steroid injection(s) within 8 weeks before the Day 364 (Week 52) visit will be defined as a treatment failure.
k. The dose of existing immunosuppressive/immunomodulatory agents may be increased, as clinically required, up to the Day 112 (Week 16) visit.
l. After the Day 112 (Week 16) visit, any increase in immunosuppressive/immunomodulatory agents dose above the baseline or Day 112 (Week 16) visit dose, whichever is higher, will cause the subject to be declared a treatment failure.
m. Starting any new immunosuppressive/immunomodulatory agent after Day 0 will cause the subject to be declared a treatment failure.
n. NSAIDs may be given as clinically indicated until the Day 308 (Week 44) visit.
o. For subjects who never received an NSAID between the Day 0 and Day 308 (Week 44) visit, starting a new NSAID after the Day 308 (Week 44) visit will declare the subject a treatment failure unless the NSAID is given for < 1 week.
p. Daily doses of aspirin up to 1000 mg/day are allowed at any time during the study.

q. For subjects who never received an aspirin regimen at a dose > 1000 mg/day between the Day 0 and Day 308 (Week 44) visit, starting a new aspirin regimen at a dose > 1000 mg/day after the Day 308 (Week 44) visit will declare the subject a treatment failure unless the aspirin is given for < 1 week.
r. Daily doses of aspirin above 1000 mg/day may be initiated at any time up to Day 308 (Week 44) visit and may continue through the end of the study.
s. A new anti-malarial (eg, hydroxychloroquine, chloroquine, quinacrine) may be started between Day 0 and the Day 112 (Week 16) visit. The dose may be increased as clinically required, up to the Day 112 (Week 16) visit, and may be reduced anytime during the study.
t. An antimalarial treatment will be considered **NEW** if the subject did not receive an antimalarial at any time during the Day 0 to Day 112 (Week 16) treatment interval.
u. After the Day 112 (Week 16) visit, any increase in dose of an anti-malarial above the baseline (Day 0) or Day 112 (Week 16) visit dose, whichever is higher, will declare the subject a treatment failure. Starting any new anti-malarial treatment after the Day 112 (Week 16) visit will declare the subject a treatment failure.

Appendix 3 Columbia Suicide-Severity Rating Scale (C-SSRS) Baseline/Screening



Appendix 4 Columbia Suicide-Severity Rating Scale (C-SSRS) Since Last Visit



Appendix 5 SELENA SLEDAI Disease Assessment Scales

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.

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

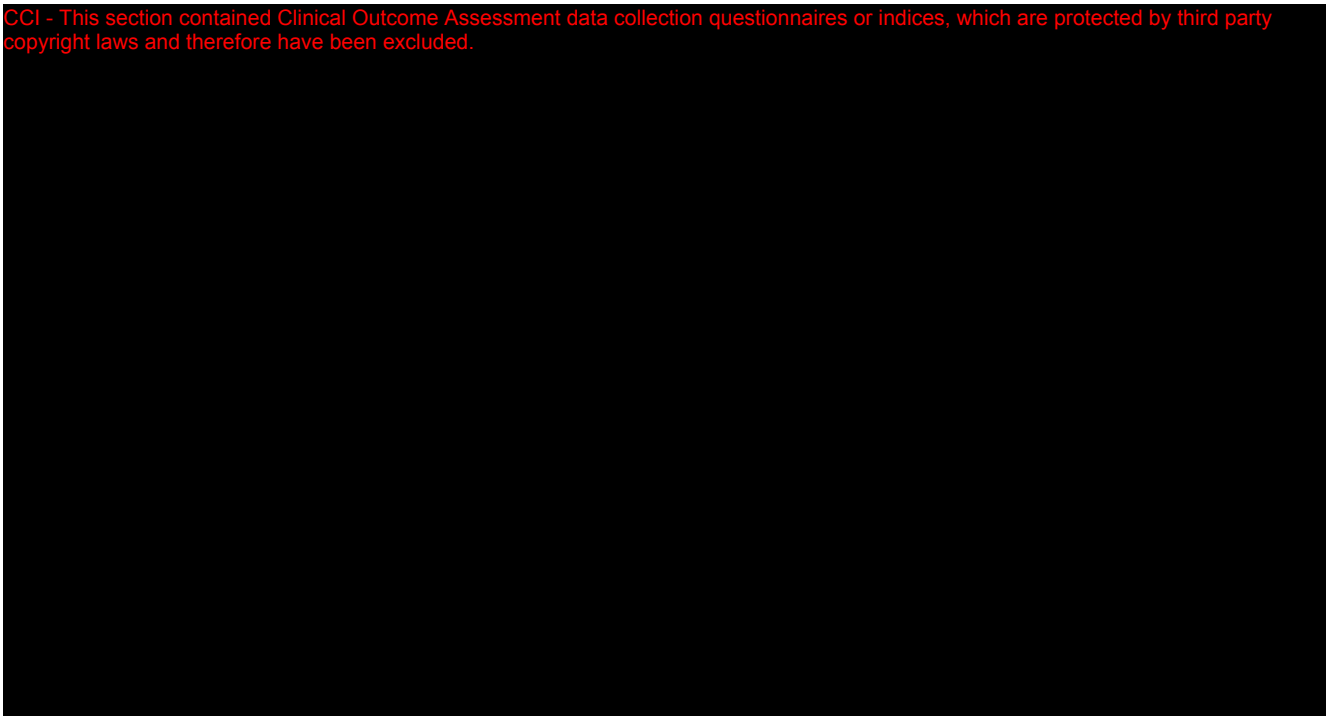
Adapted from:

Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus 1999; 8:685-691.

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



Appendix 6 Draft Recommendations for Steroid Dosing and Tapering

Table 11-1 depicts the 2 main clinical groups of major SLE presentations where steroids would be used. Table 11-2 summarizes the recommended steroid dosing and tapering.

Table 11-1 Major SLE presentations where steroids would be used

	SEVERE	MODERATELY SEVERE
Central Nervous System	cerebral vasculitis encephalitis psychosis coma transverse myelitis	chorea peripheral neuropathy pseudotumor orbit optic neuritis retinitis encephalopathy autoimmune sensorineural hearing loss mononeuritis multiplex status epileliticus demyelinating syndrome lupoid
Cardiopulmonary	pneumonitis pulmonary hemorrhage cardiac tamponade myocarditis coronary arteritis	Pneumonitis pulmonary effusion shrinking lung pericarditis myocarditis
Cutaneous	thrombotic thrombocytopenia purpura	severe discoid severe oral ulcers diffuse subacute cutaneous lupus bullous skin disease cutaneous vasculitis
Renal	rapidly progressive glomerulonephritis	Glomerulonephritis ureteral obstruction
Gastrointestinal	mesenteric vasculitis	pancreatitis peritonitis lupus colitis severe hepatitis protein losing enteropathy
Hematologic	idiopathic thrombocytopenia (< 15,000 platelets/mm^3)	Thrombocytopenia (15-30,000 platelets/mm^3) hyperviscosity hemophagocytic syndrome lupus adenitis (a la kikochi) hemolytic anemia

	SEVERE	MODERATELY SEVERE
Musculoskeletal		polychondritis polyarthritis
Miscellaneous		fever

Table 11-2 Recommended, standardized initial steroid dosing and steroid tapering

	Dose* Induction (Median)	Range	Mean ± SD	Duration of Induction Therapy (Median)	Duration to Off Steroids (Median)
Severe SLE	60 PO	40-100	66.4 ± 15.5	14 days	20 weeks
	1000 bolus	40-1000	766 ± 344	3 days	-
Moderately Severe SLE	35 PO	15-75	38.5 ± 13.4	7 days	15 weeks
Mild SLE	10 PO	0-30	14.5 ± 6.8	not detectable	not detectable

*Prednisone dose in mgs for a 70-kilogram person.

(From: Response Criteria for Systemic Lupus Erythematosus Clinical Trials: Steroid Sparing Ability of an Intervention-Working Draft; Prepared for The American College of Rheumatology; September 10, 2002). Not endorsed by ACR.

Appendix 7 BILAG

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 8 FACIT-Fatigue Scale (Version 4)

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 SLICC/ACR Damage Index

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 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)*

Urinalysis

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

Spot Urine (protein : creatinine ratio)
Urine Pregnancy

Biological Markers

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)

BLyS protein
Serum complement (C3, C4)

Immunoglobulins

Serum immunoglobulin isotypes: IgG, IgM, IgA

PK and Immunogenicity

Belimumab pharmacokinetic assessment
Belimumab immunogenicity assessment

Autoantibodies

ANA titer and OD
Anti-dsDNA
aCL
Lupus anticoagulant
±beta-2-glycoprotein-1**
ENAs**

*Refer to Table 6-1 and Table 6-2 for assessment time points
**May be collected in selected sites/regions

Modified Chem-20

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

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

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

Estimated Creatinine Clearance/ GFR (Cockcroft-Gault)

Other Screening Labs

HIV-1/2 antibody
Hepatitis C antibody
HBsAg and HB Core antibody
Serum pregnancy
Alcohol and Drug screen
PT / PTT

Liver event follow-up assessments:

- Hepatitis A IgM antibody
- HBsAg and HB Core antibody (IgM)
- Hepatitis C RNA
- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody
- Hepatitis E IgM antibody
- CPK
- Anti-smooth muscle antibody
- Type 1 anti-liver kidney microsomal antibodies

Appendix 11 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 (~6 to 8 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, SLE 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 investigational product, 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 12 Adverse Event Severity Grading Tables

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

(continued)

*ULN = Upper Limit of Normal.

Modified from DMID Adult Toxicity Tables, 2001

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

(continued)

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 < 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 13 Liver Safety Required Actions and Follow up Assessments

Phase III-IV 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).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria - Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td colspan="2">ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td colspan="2">ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks
ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td colspan="2">ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the 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</td><td>• Viral hepatitis serology[4]
• Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]
• Blood sample for pharmacokinetic (PK) analysis, obtained within approximately 1 to 2 weeks after the liver event [6]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
• Fractionate bilirubin, if total</td></tr>
</table>

granted (refer to Appendix 14) • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct 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.

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).

4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody.
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for 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 study reference manual.

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss 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 • 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.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.
Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

Appendix 14 Liver Safety – Study Treatment Restart Guidelines

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

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments,

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

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (eg, biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

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, possible study treatment-induced liver injury) or study treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) 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.

Protocol Number: HGS1006-C1112
Amendment 02, Date: 09 February 2017

Protocol Title: A Phase 3/4, Multi-Center, Randomized, Double-Blind, Placebo Controlled, 52 Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Adult Subjects of Black Race with Systemic Lupus Erythematosus (SLE)

Summary of Modifications and Rationale:

1. The sample size for this study has been reduced from 816 subjects to approximately 501 subjects due to pragmatic considerations to address the study objectives for this post marketing commitment trial within a reasonable timeframe and based on updated information from studies BEL112341 (HGS1006-C1115/BLISS SC) and BEL113750 (Northeast Asia) regarding the assumed treatment differences. This modification has been made in consultation with the US Food and Drug Administration and European Medicines Agency.

2. The following has been revised in the Synopsis and Section 8:
   - The primary efficacy endpoint has been changed to the SRI response rate with the SELENA SLEDAI modified for SLEDAI-2K scoring for proteinuria. The original endpoint of the SRI with the SELENA SLEDAI scoring for proteinuria will be a major secondary endpoint. (Note: the proteinuria scoring modification occurs programmatically and does not impact the current scoring for individual subjects by the site.)
   - For other efficacy endpoints, clarification regarding the use of modified SLEDAI-2K scoring for proteinuria and SELENA SLEDAI scoring for proteinuria in the endpoint and its analysis has been added or modified accordingly.
3. The following selection criteria have been revised or clarified in the Synopsis and Section 4:
   - Revisions intended to allow more subjects to be considered for enrollment:
     - The inclusion criterion for having an unequivocally positive autoantibody test has been qualified to allow a HEp-2 immunofluorescence assay (IFA) and/or positive enzyme immunoassay (EIA) result as evidence and to allow a historically positive anti-dsDNA result to have confirmation by any validated commercial assay.
     - The exclusion criterion for prior B cell targeted therapies has been modified from a lifetime exclusion to allowance of a 1 year or more ago. Literature evidence supports that the majority of patients have largely recovered from immunosuppressive effects of B cell depletion within 1 year after treatment with B cell targeted therapy.
     - In the exclusion criterion for anti-TNF therapies, 2 other examples were added to the list.

- In the exclusion criterion for Grade 3 lab AEs, the list of exceptions was modified to allow subjects with stable Grade 3 prothrombin time (PT) secondary to anticoagulant treatment.
- In the exclusion criterion for Grade 3 lab AEs, the list of exceptions was expanded to allow subjects with stable Grade 3 hemoglobin reduction due to lupus.

- Modifications to be consistent with GSK standards:
  - The inclusion criterion for female subjects has been modified to be consistent with GSK standards. A separate section (Section 4.3) on contraception recommendations has been added.
  - The exclusion criterion for hepatitis B infection has been modified to be consistent with GSK standards to test for hepatitis B core antibody, in addition to hepatitis B surface antigen.

4. The following safety sections have been modified to be in alignment with the belimumab program standard text:
   - A benefit and risk assessment for belimumab has been added.
   - Information on non-acute delayed type hypersensitivity reaction and symptoms has been added.
   - The adverse events section has been modified throughout for consistency with AE and SAE, and pregnancy data collection procedures and forms.
   - Progressive multifocal leukoencephalopathy (PML) text has been updated.
   - The section on liver safety evaluation has been replaced to be consistent with GSK standards. Restart criteria and monitoring have been added. New associated appendices have been added and the Laboratory appendix was updated accordingly.

5. The following conduct sections have been modified or added:
   - The study agent infusion dosing time has been clarified from “over 1 hour” to “over no less than 1 hour”, which was the intent of the original protocol.
   - The concomitant medication section has been modified to clarify use of prohibited medications and treatment failures.
   - Missing 3 or more consecutive doses of study agent, before administration of live vaccine, and Sponsor discretion have been added to the list of reasons for treatment withdrawal.
   - Pragmatic flexibility has been added to the dosing visit and dosing schedule, to allow patients who are identified to have reached withdrawal criteria at completion of the double blind portion of the protocol (week 52) to enter the open-label phase of the study pending consultation with the medical monitor.
   - Pragmatic flexibility has been added to using the prior visit weight measurement in lieu of the same day weight measurement for dose calculation. If the two

weights vary by more than 10% then the current visit weight measurement must be used.

- The survival assessment language has been updated from determination at Week 52 to determination at approximately 52 weeks after the first dose of study agent.
- The communication process for an unblinding event has been clarified.
- Collection of an immunogenicity sample has been removed at the 6 month follow-up for subjects with positive response at 8-week follow-up. Collection of the follow-up samples is no longer necessary based on current immunogenicity safety profile and anticipated low clinical utility. Thus, Section 6.8 1.1 Immunogenicity (6-Month Follow-Up) has been deleted which resulted in the renumbering of subsequent sections. These renumbering changes are not shown in the Modifications section below, except for the renumbering change that affected Inclusion Criterion 4.
- A urine pregnancy test has been added at the 8-week follow-up visit for all women of child bearing potential. Also an instruction has been added that 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. Sections of the protocol affected by this change have been modified accordingly.
- The IDMC section has been edited for clarity regarding timing of the reviews.

6. Administrative updates have been made as follows:
   - The study sponsor street address has been updated on the cover page.
   - A page with the protocol's revision chronology has been added.
   - Level 5 headings are now in bold type face. These minor changes are not shown in the Modifications section below.
   - The presentation of cross-referencing sections, e.g., "see Sections X.1 and Y.2" was changed to "see Section X.1 and Section Y.2". These minor changes are not shown in the Modifications section below.
7. Administrative changes/corrections of typographical errors have been made as appropriate, including corrections to Appendix 1 (The ACR Criteria for the Classification of Systemic Lupus Erythematosus) and Appendix 11 (Pharmacogenetic Research).

Associated Protocol Modifications:

~~Strikethrough~~ indicates deleted text; **bold** indicates new/replacement text when text has been modified**.** When a new section/text is preceded by "*Added:"* as all text is new, bold text indicates bolded text within the new section.

Cover Page:

Formerly:

Protocol Amendment: 01
Date: 20 June 2012

STUDY SPONSOR, line 2: ~~14200 Shady Grove Road~~

Modified to:

Protocol Amendment: 0**2**
Date: **09 February 2017**

STUDY SPONSOR, line 2: **9910 Belward Campus Drive**

Added:

REVISION CHRONOLOGY FOR HGS1006-C1112 (BEL115471)

	Date	**Document***
Global	21 November 2011	Original
Global	20 June 2012	Amendment No 01
Local 2014N219219_00	02 February 2015	Local Amendment 01 for France
Global 2014N199062_00	09 February 2017	Amendment No 02

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

Synopsis Diagnosis & Inclusion Criteria and Section 4.1 Inclusion Criteria

Formerly:

4. Have active SLE disease defined as a SELENA SLEDAI score ≥ 8 at screening (refer to Appendix 5 and Section ~~6.9.1.1~~ Scoring for Proteinuria for Eligibility at Screening).

5. Have unequivocally positive autoantibody test results defined as a~~n~~ ANA titer ≥ 1:80 and/or a positive anti-dsDNA (≥ 30 IU/mL) serum antibody test ~~from 2 independent time points~~ as follows:
   - ~~Positive test results~~ from 2 independent time points within the study screening period. Screening results must be based on the study's central laboratory results.

     OR

- One positive historical test result and 1 positive test result during the screening period.
- Historical documentation of a positive ~~test of~~ ANA (eg, ~~ANA by~~ HEp-2 ~~titer~~) or anti-dsDNA (eg, anti-dsDNA by ~~Farr~~ assay) must include the date and type of the test, the name of the testing laboratory, numerical reference range, and a key that explains values provided as positive vs negative OR negative, equivocal/borderline positive). Only unequivocally positive values as defined in the laboratory's reference range are acceptable; borderline values will not be accepted.

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 the 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.~~

     ~~NOTE: MMF and other forms of mycophenolate affect the metabolism of oral contraceptives and may reduce their effectiveness. As such, women receiving mycophenolate who are using oral contraceptives for birth control should employ an additional method (eg, barrier method).~~

Modified to:

4. Have active SLE disease defined as a SELENA SLEDAI score ≥ 8 at screening (refer to Appendix 5 and Section **6.8.1.1** Scoring for Proteinuria for Eligibility at Screening).

5. Have **2** unequivocally positive autoantibody test results defined as a **positive antinuclear antibody** (ANA) **test** [**ie, a** titer ≥ 1:80 **by HEp-2 immunofluorescence assay (IFA) and/or positive enzyme immunoassay (EIA)**] and/or a positive anti-dsDNA (≥ 30 IU/mL) serum antibody test as follows:
   - from 2 independent time points within the study screening period. Screening results must be based on the study's central laboratory results.

   OR

   - One positive historical test result and 1 positive test result during the screening period.
   - Historical documentation of a positive ANA **test** (eg, HEp-2 **IFA or EIA**) or anti-dsDNA (eg, anti-dsDNA by **any validated commercial** assay) must include the date and type of the test, the name of the testing laboratory, numerical reference range, and a key that explains values provided as positive vs negative OR negative, equivocal/borderline positive). Only unequivocally positive values as defined in the laboratory's reference range are acceptable; borderline values will not be accepted.

7. A female subject is eligible to enter the study if she is:
   - Not pregnant or nursing;
   - Of non-childbearing potential **defined as**
     - **pre-menopausal females with a documented tubal ligation, hysterectomy, documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion, or documented bilateral oophorectomy or**
     - **postmenopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile [eg, > 45 years, in the absence of hormone replacement therapy or other cause for amenorrhea]; in questionable cases obtain a blood sample for follicle stimulating hormone (FSH) and estradiol simultaneously to confirm. Diagnostic levels for FSH and estradiol vary by specific laboratories/assays;**
   - **OR is of child-bearing potential with negative pregnancy test as determined by serum human chorionic gonadotrophin (hCG) test at screening and urine hCG test prior to dosing AND**
     - **Agrees to use one of the contraception methods listed in the protocol (see Section 4.3) for 2 weeks prior to the day of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until 16 weeks following the last dose of study agent.**
     - **OR has only same-sex partners, when this is her preferred and usual lifestyle.**

Synopsis Diagnosis & Inclusion Criteria and Section 4.2 Exclusion Criteria

Formerly:

1. Have received 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, anti-BAFF (LY2127399), or~~ anti-BLyS [belimumab]) at any time.

2. Have received any of the following within 364 days of Day 0:
   - Abatacept.
   - A biologic investigational agent other than B cell targeted therapy (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.)

4. Have received any of the following within 90 days of Day 0:
   - Anti-TNF therapy (eg, adalimumab, etanercept, infliximab).
   - Intravenous (IV) cyclophosphamide
   - Interleukin-1 receptor antagonist (anakinra).
   - Intravenous immunoglobulin (IVIG).
   - High dose prednisone or equivalent (> 100 mg/day).
   - Plasmapheresis.

16. Have a historically positive test or test positive at screening for HIV antibody, hepatitis B surface antigen, or hepatitis C antibody.

18. Have a Grade 3 or greater laboratory abnormality based on the Adverse Event Severity Grading Tables (Appendix 12) except for the following that are allowed:
   - 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 3/4 proteinuria (≤ 6 g/24 hour equivalent by spot urine protein to creatinine ratio allowed).
   - Stable Grade 3 hypoalbuminemia due to lupus nephritis, and not related to liver disease or malnutrition.
   - 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 ALT and/or AST must be ≤ Grade 2.
   - Stable Grade 3 neutropenia or stable Grade 3 white blood cell count.

Modified to:

1. Have received treatment with anti-BLyS [belimumab]) at any time.

2. Have received any of the following within 364 days of Day 0:

- Abatacept.
- **Other B cell targeted therapy (eg, rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI-Fc, or anti-BAFF (LY2127399).**
- A biologic investigational agent other than B cell targeted therapy (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.)

4. Have received any of the following within 90 days of Day 0:
   - Anti-TNF therapy (eg, adalimumab, **certolizumab pegol,** etanercept, **golimumab**, infliximab).
   - Intravenous (IV) cyclophosphamide.
   - Interleukin-1 receptor antagonist (anakinra).
   - Intravenous immunoglobulin (IVIG).
   - High dose prednisone or equivalent (> 100 mg/day).
   - Plasmapheresis.

16. Have a historically positive test or test positive at screening for HIV antibody, hepatitis B surface antigen **(HBsAg), hepatitis B core antibody**, or hepatitis C antibody.

18. Have a Grade 3 or greater laboratory abnormality based on the Adverse Event Severity Grading Tables (Appendix 12) except for the following that are allowed:
   - Stable Grade 3 prothrombin time (PT) secondary to **anticoagulant, eg,** 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 3/4 proteinuria (≤ 6 g/24 hour equivalent by spot urine protein to creatinine ratio allowed).
   - Stable Grade 3 hypoalbuminemia due to lupus nephritis, and not related to liver disease or malnutrition.
   - 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 ALT and/or AST must be ≤ Grade 2.
   - Stable Grade 3 neutropenia or stable Grade 3 white blood cell count.
   - **Stable Grade 3 hemoglobin reduction due to lupus.**

Synopsis – Study Design and Schedule and Section 3 Study Design, paragraph 1

Formerly:

Approximately ~~816~~ SLE subjects will be randomized with a target of ~~about 544~~ subjects treated with belimumab and ~~272~~ subjects receiving placebo.

Modified to:

Approximately **501** SLE subjects will be randomized with a target of **at least 334** subjects treated with belimumab and **167** subjects receiving placebo.

Synopsis – Study Design and Schedule, Section 3 Study Design, paragraph 2

Formerly:

Study agent will be administered IV over 1 hour.

Modified to:

Study agent will be administered IV over **no less than** 1 hour.

Synopsis – Efficacy Endpoints and Analysis and Section 8.5.1 Primary Efficacy Endpoint

Formerly:

The primary efficacy endpoint is the systemic lupus erythematosus responder index (SRI) at Week 52.

A SRI response is defined as:

- ≥ 4 point reduction from baseline in SELENA SLEDAI score,

  AND

- No worsening (increase of < 0.30 points from baseline) in Physician's Global Assessment (PGA),

  AND

- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (ie, at Week 52).

Modified to:

The primary efficacy endpoint is the systemic lupus erythematosus responder index (SRI) **response rate with the modified SLEDAI-2K scoring for proteinuria** at Week 52.

A SRI response is defined as:

- ≥ 4 point reduction from baseline in SELENA SLEDAI score **(with the modified SLEDAI-2K scoring for proteinuria),**

  AND

- No worsening (increase of < 0.30 points from baseline) in Physician's Global Assessment (PGA),

AND

- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (ie, at Week 52).

Synopsis – Efficacy Endpoints and Analysis and Section 8.5.3 Secondary Efficacy Endpoints

Formerly:

~~1.~~ Time to first severe flare (as measured by the modified SLE Flare Index).
~~2.~~ Percent of subjects whose average prednisone dose has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52, in subjects receiving greater than 7.5 mg/day at baseline.

Modified to:

1. SRI response rate with the SELENA SLEDAI for scoring of proteinuria at Week 52.
2. Time to first severe flare (as measured by the modified SLE Flare Index)**; with SLEDAI-2K and SELENA SLEDAI as the SLEDAI criterion of the SFI.**
3. Percent of subjects whose average prednisone dose has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52, in subjects receiving greater than 7.5 mg/day at baseline.

Synopsis Sample Size Calculation

Formerly:

Approximately ~~816~~ subjects will be randomized and treated in the study, with a target of at least ~~544~~ subjects in the arm receiving belimumab and ~~272~~ subjects in the arm receiving placebo. This sample size provides at least 90% power at a 5% level of significance to detect a minimum of a ~~12%~~ absolute improvement in the response rate for the 10 mg/kg belimumab group ~~(assumed rate = 56%)~~ relative to the placebo group (assumed rate = ~~44%~~) at Week 52. The selection of t~~he 12% absolute improvement is evidence-based and is based on the observed response rate in the Phase 3 studies [BLISS 76 (HGS1006-C1056) and BLISS-52 (HGS1006-C1057)]. The sample size calculation uses the most conservative estimate for the standard deviation (SD) in the population (ie, population SD = 50%)~~.

Modified to:

Approximately **501** subjects will be randomized and treated in the study, with a target of at least **334** subjects in the arm receiving belimumab and **167** subjects in the arm receiving placebo. This sample size provides at least 90% power at a 5% level of significance to detect a minimum of a **15.55%** absolute improvement in the **SRI** response

rate **with the modified SLEDAI-2K scoring for proteinuria** for the 10 mg/kg belimumab group relative to the placebo group (assumed rate = **43.95%**) at Week 52. **This sample size is also sufficient to provide approximately 80% power at a 5% level of significance to detect a minimum of a 13.4% absolute improvement in the SRI response rate with the SELENA SLEDAI scoring for proteinuria for the 10 mg/kg belimumab group relative to the place group (assumed rate = 44.8%).**

The selection of **these assumed treatment differences is based on the observed SRI data from studies BEL112341 (HGS1006-C1115/BLISS SC) and BEL113750 (Northeast Asia), which are two efficacy studies that concluded in 2015 and 2016, respectively, and have nearly identical eligibility criteria to study HGS1006-C1112 including requiring a screening SS score ≥8.**

Synopsis Analysis of Major Secondary Efficacy Endpoints

Added:

The SRI response rate with the SELENA SLEDAI scoring for proteinuria at Week 52 will be compared between the belimumab treatment group and the placebo group using the same analysis methods as described for the primary endpoint.

Synopsis Safety Endpoints and Analysis

Formerly:

An ~~i~~ndependent Data Monitoring Committee (DMC) will review unblinded safety data on an ongoing basis until data ~~through Week 52~~ are locked and analyzed ~~(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 1st DMC data review meeting will occur after the first 100 subjects have been treated through Day 56 or ~~approximately~~ 6 months ~~after~~ the treatment of the 1st subject, whichever is earlier. After the initial review, the committee will review the data approximately every 6 months. ~~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 52 and the 6-month open-label extension portion of the study.~~ Investigators will be notified of the outcome of each DMC meeting.

Modified to:

An **I**ndependent Data Monitoring Committee (**I**DMC) will review unblinded safety data **for this study** on an ongoing basis until **the** data are locked and analyzed **through Week 52**. The **I**DMC will include at least 3 physicians, and a statistician, none of whom are affiliated with the sponsor. **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. The 1st IDMC data review meeting will occur after the first 100 subjects have been treated through Day 56 or **within** 6 months **of** the treatment of the 1st subject, whichever is earlier. After the initial review, the committee will review the data approximately every 6 months. Investigators **and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), as appropriate,** will be notified of the outcome of each IDMC meeting.

Synopsis Immunogenicity and Section 6.8.4 Immunogenicity

Formerly:

Serum samples for anti-belimumab antibody measurements will be obtained from all randomized subjects before administration of study agent on Days 0, 56 (Week 8), 168 (Week 24), 364/Exit (Week 52), and 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.~~

Modified to:

Serum samples for anti-belimumab antibody measurements will be obtained from all randomized subjects before administration of study agent on Days 0, 56 (Week 8), 168 (Week 24), 364/Exit (Week 52), and at the 8-week follow-up visit.

List of Abbreviations

Added:

EIA	Enzyme immunoassay
HB	Hepatitis B
HBsAg	Hepatitis B surface antigen
hCG	human chorionic gonadotrophin
IDMC	Independent Data Monitoring Committee
JCV	John Cunningham virus
µL	microliter
PASS	Power Analysis and Sample Size

Section 1.3.2 Choice of Target Patient Population

Formerly:

The target population to be enrolled in this trial will be adult subjects of self-identified black race with a clinical diagnosis of SLE according to the ACR criteria. These subjects must have active disease defined as a SELENA SLEDAI score ≥ 8 at screening, and be positive for autoantibodies, defined as ANA ~~titer ≥ 1:80~~, and/or anti-dsDNA (≥ 30 IU/mL) at 2 time points prior to randomization.

Modified to:

The target population to be enrolled in this trial will be adult subjects of self-identified black race with a clinical diagnosis of SLE according to the ACR criteria. These subjects must have active disease defined as a SELENA SLEDAI score ≥ 8 at screening, and be positive for autoantibodies, defined as **a positive** ANA **test**, and/or anti-dsDNA (≥ 30 IU/mL) at 2 time points prior to randomization.

Section 1.3.3 Rationale of Choice of Primary Endpoint for Efficacy

Formerly:

The primary efficacy endpoint is response by the SLE responder index (SRI) at Week 52.

Modified to:

The primary efficacy endpoint is response by the SLE responder index (SRI) **response rate with the modified SLEDAI-2K scoring for proteinuria** at Week 52.

Section 1.3.4 Rationale for Dose and Schedule

Formerly:

The dose and schedule to be studied is 10 mg/kg administered as an IV infusion over ~~a period of~~ 1 hour, at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

Modified to:

The dose and schedule to be studied is 10 mg/kg administered as an IV infusion over **no less than** 1 hour, at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

New Section for Benefit-Risk Assessment

Added:

Section 1.4 Benefit-Risk Assessment

Section 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 non opportunistic infections. Potential risks (ie, 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, 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 dyspnoea. However, infusion and hypersensitivity reactions can be severe and fatal. Most clinical trial and spontaneous cases of serious hypersensitivity occurred during or within the first hour after the completion of the infusion, although some cases report delayed acute onset (>4 hours but <4 days) or a delayed non-acute onset (4-21 days) hypersensitivity reactions.

Infections have been reported with administration of belimumab and are also associated with both SLE and immunosuppressant medication used to treat SLE. The mechanism of action of belimumab may increase the potential risk for the development of infections. In the phase 2 and 3 clinical trials, there was a slight increase in the overall rate of infections in the belimumab group compared with the placebo group. There was no difference in the rate of serious infections, infections leading to discontinuation, or infections of special interest. Out to 10 years in the Phase 2 and 3 continuation studies, the incidence rate of serious infections has remained stable or declined over time.

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. Delays 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.
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	Exclude patients with any of the following: currently on any suppressive therapy for a chronic infection; hospitalization for treatment of an infection within 60 days of Day 0; use of IV or IM	Monitor patients for signs and symptoms of infection, monitor laboratory values, request that patients report signs of infection. Treat infections immediately and appropriately.

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
	placebo were nasopharyngitis, bronchitis, pharyngitis, cystitis, and gastroenteritis viral. Serious infections occurred in 5% of patients receiving either belimumab or placebo.	antibiotics within 60 days of Day 0; a history of or positive test at screening for HIV, hepatatis B or hepatitis C; have Grade 3 or 4 lymphopenia; or have Grade 3 or 4 IgG or IgA deficiency	
Progressive multifocal leukoencephalopathy (PML)	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.		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.	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.
Immunogenecity	As with other monoclonal antibodies, treatment with belimumab could lead to the development of anti-drug antibodies		Monitor anti-drug antibody laboratory values.

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
	(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.		
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 immunisations. 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 immunisations received prior to administration of belimumab.	Exclude patients who have received a live vaccine within 30 days of Day 0.	Do not administer live vaccines concurrently.
Potential	There have been reports of depression	Exclude patients who have	Monitor patients for signs and symptoms of

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
psychiatric events - Depression and suicidality	and suicidality in patients receiving belimumab. 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].	evidence of serious suicide risk including any history of suicidal behaviour 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.	psychiatric events including depression and suicidality, request that patients report signs and symptoms. Treat appropriately

Refer to Section 8.3 for information about the Independent Data Monitoring Committee (IDMC) being used in the study.

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 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. 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).

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.

New Section 4.3

Added:

Section 4.3 Contraception Requirements for Female Subjects

Female subjects of childbearing potential must not become pregnant during the study and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%. Female subjects of childbearing potential with same sex partners (when this is their preferred and usual lifestyle) are not required to be abstinent or to use contraception.

Abstinence
Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (eg calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of < 1%

- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen

- Implants of levonorgestrel or etonogestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) with <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository).

NOTE: MMF and other forms of mycophenolate affect the metabolism of oral contraceptives and may reduce their effectiveness. As such, women receiving mycophenolate who are using oral contraceptives for birth control should employ an additional method (eg, barrier method).

NOTE: These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Section 5.2 Packaging, Labeling, Preparation, and Storage, paragraph 6

Formerly:

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 current body weight in kilograms (kg) obtained at each visit prior to dosing.

Modified to:

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 current body weight in kilograms (kg) obtained at each visit prior to dosing. **At sites where it is impractical to use the subject's current body weight to calculate the dose, it is permissible for the Week 2 visit onward to use the subject's body weight from the previous visit (eg, the Day 0 weight can be used to calculate the dose for the Week 2 visit). However, the subject's body weight will be measured prior to dosing and if the previous visit weight and current visit weight vary by more than 10% then the weight measured at the current visit must be used.**

Section 5.3 Dose, Route of Administration, and Schedule, paragraph 1

Formerly:

All study agent treatments will be administered IV over 1 hour.

Modified to:

All study agent treatments will be administered IV over **no less than** 1 hour.

Section 5.3 Dose, Route of Administration, and Schedule, paragraph 4

Formerly:

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 phase and the 6-month open-label extension. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing any untoward reactions. Beyond the first 2 infusions, subjects should be monitored during and for an appropriate period of time after infusion according to the study sites' guidelines or standard operating procedure for IV infusions.

Modified to:

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 phase and the 6-month open-label extension. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing any untoward reactions. **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 the study sites' guidelines or standard operating procedure for IV infusions.

Section 5.4 Alteration of Dose/Schedule Due to Toxicity, paragraph 2

Formerly:

If a subject experiences a clinically significant AE that the investigator believes may be possibly~~, probably, or definitely~~ 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.

Modified to:

If a subject experiences a clinically significant AE that the investigator believes may be possibly 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.

Section 5.4 Alteration of Dose/Schedule Due to Toxicity, paragraph 3

Formerly:

If a subject experiences a clinically significant, potentially *life-threatening* (Grade 4) AE that the investigator believes may be possibly~~, probably, or definitely~~ 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 the protocol and also~~ until resolution of the AE(s) ~~(whichever is longer)~~. The subject must also return for an Exit visit 4 weeks after the last administration of study agent and a follow-up visit 8 weeks after the last administration of study agent.

Modified to:

If a subject experiences a clinically significant, potentially *life-threatening* (Grade 4) AE that the investigator believes may be possibly related to study agent, then treatment with study agent will be discontinued. The subject should be withdrawn from the study agent and followed until resolution of the AE(s). The subject must also return for an Exit visit 4 weeks after the last administration of study agent and a follow-up visit 8 weeks after the last administration of study agent. **An attempt will be made to ascertain survival status approximately 52 weeks after the first dose of study agent.**

Section 5.5 Concurrent Medications

Formerly:

This section reviews the medications and the doses allowed and prohibited during the course of the study. Any time the concurrent medication ~~guidelines~~ are not followed, subjects are ~~to be withdrawn from the study and will be~~ considered treatment failures (refer to Appendix 2).

~~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.

Modified to:

This section reviews the medications and the doses allowed and prohibited during the course of the study. Any time the concurrent medication **requirements** are not followed, subjects are considered treatment failures (refer to Appendix 2). **Subjects who meet a treatment failure criterion prior to completing IP administration at Week 48 should**

be withdrawn from IP and not permitted to enter the 6-month open-label extension of the protocol. The subject must return for an Exit visit 4 weeks after the last administration of study agent and a follow-up visit 8 weeks after the last administration of study agent. An attempt will be made to ascertain survival status approximately 52 weeks after the first dose of study agent. If a subject completes all IP dosing through Week 48 of the protocol, and at the Week 52 protocol visit it is determined that a subject has met a treatment failure criterion, the subject should complete the Week 52 assessments in the double-blind period, and after consultation with the Medical Monitor, consideration may be given for the subject to enter into the 6-month open-label extension. The subject will still be deemed a treatment failure from the date the criterion was met for analysis purposes.

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

Section 5.5.1 Allowable Medications, paragraph 2

Formerly:

Once the subject is randomized and receives the 1st dose of study agent on Day 0, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically required; however, changes in certain medications (as outlined below) may result in the subject being defined as a treatment failure and ~~will~~ require withdrawal from the study.

Modified to:

Once the subject is randomized and receives the 1st dose of study agent on Day 0, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically required; however, changes in certain medications (as outlined below) may result in the subject being defined as a treatment failure and **may** require withdrawal from the study **following consultation with the medical monitor (see Section 5.5)**.

Section 5.5.1.2.1 Systemic Steroids for SLE-related Disease Activity, List Bullets 2, 3 and 4

Formerly:

- Within 8 weeks before the Day 364 (Week 52) visit, no new increase over the baseline (Day 0) or Day 308 (Week 44) visit dose, whichever is higher, is allowed.

Modified to:

- Within 8 weeks before the Day 364 (Week 52) visit, no new increase over the baseline (Day 0) or Day 308 (Week 44) visit dose, whichever is higher, is allowed. **A new increase would deem the subject a treatment failure.**

Section 5.5.1.2.3 Steroids for Reasons Other Than SLE Disease Activity, From Days 168 to 308 (Weeks 24 to 44) Visits:

Formerly:

Steroids may be given for reasons other than SLE disease activity from the Day 168 (Week 24) visit until the Day 308 (Week 44) visit at any dose/duration that does not result in a total steroid dose (for SLE and non-SLE reasons) > 25% or > 5 mg, whichever is higher, over the baseline dose. In addition, steroids for non-SLE reasons may be given short-term at higher doses according to the following guidelines:

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

and/or

- Up to 100 mg/day (prednisone) for 2-3 days ,

and/or

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

The duration of high dose steroids use for reasons other than SLE must not exceed 7 days, after which time, tapering should begin. The total steroid dose must be tapered to within 25% or 5 mg over the baseline dose, whichever is higher, within 30 days of the 1st dose of a course of steroids. In addition, the steroid dose must be tapered to within 25% or 5 mg over the baseline dose, whichever is higher, by the Day 308 (Week 44) visit.

Modified to:

Steroids may be given for reasons other than SLE disease activity from the Day 168 (Week 24) visit until the Day 308 (Week 44) visit at any dose/duration that does not result in a total steroid dose (for SLE and non-SLE reasons) > 25% or > 5 mg, whichever is higher, over the baseline dose. **Any total steroid dose exceeding this rule will deem the subject a treatment failure.** In addition, steroids for non-SLE reasons may be given short-term at higher doses according to the following guidelines:

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

and/or

- Up to 100 mg/day (prednisone) for 2-3 days ,

and/or

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

The duration of high dose steroids use for reasons other than SLE must not exceed 7 days, after which time, tapering should begin. The total steroid dose must be tapered to within 25% or 5 mg over the baseline dose, whichever is higher, within 30 days of the 1st dose of a course of steroids. In addition, the steroid dose must be tapered to within 25% or 5 mg over the baseline dose, whichever is higher, by the Day 308 (Week 44) visit. **Otherwise the subject will be deemed a treatment failure.**

Section 5.5.2 Prohibited Medications and Therapies, paragraph 1, List bullets 2, 3, and 4

Formerly:

Subjects who start prohibited medications or therapies 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:

- Co-enrollment into another study of an investigational agent or that may interfere with the conduct of this protocol.
- Anti-TNF therapy (eg, adalimumab, etanercept, infliximab).
- Other biologics (eg, rituximab, abatacept, interleukin-1 receptor antagonist [anakinra]).

Modified to:

Subjects who start prohibited medications or therapies 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 **an Exit visit 4 weeks after the last administration of study agent and a follow-up visit 8 weeks after the last administration of study agent. In addition, an attempt will be made to ascertain survival status approximately 52 weeks after the first dose of study agent.**

- Co-enrollment into another study of an investigational agent or **another study** that may interfere with the conduct of this protocol.
- Anti-TNF therapy (eg, adalimumab, **certolizumab pegol,** etanercept, **golimumab,** infliximab).
- Other biologics (eg, rituximab, abatacept, interleukin-1 receptor antagonist [anakinra], **tocilizumab**).

Section 6.1 Screening Procedures (Day -35 to Day 0), List Bullet 7

Formerly:

- Blood samples for: (see Appendix 10 – Laboratory Tests)
  - HIV antibody, ~~hepatitis B surface antigen,~~ and hepatitis C antibody testing

Modified to:

- Blood samples for: (see Appendix 10 – Laboratory Tests)
  - HIV antibody, **HBsAg, HB core antibody,** and hepatitis C antibody testing.

Section 6.3 Double-blind Treatment Period, paragraphs 1 and 3

Formerly:

After the 1st month of therapy, visits to the study site for clinical evaluation, disease activity assessment, and laboratory sampling will occur every 28 days (calculated from the Day 0 dose) for a total of 48 weeks of treatment.

All subjects who withdraw from treatment prior to Week 52 will be followed for survival ~~at Week~~ 52~~, unless consent is withdrawn~~. In the event that a subject ~~discontinues study agent at any time during the study or~~ withdraws consent, an attempt ~~will~~ be made to ~~ascertain~~ survival status ~~at approximately 52 weeks after the first dose of study agent~~.

Modified to:

After the 1st month of therapy, 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) for a total of 48 weeks of treatment.

All subjects who withdraw from treatment prior to Week 52 will be followed **(eg, phone contact)** for survival 52 **weeks after the first dose of study agent**. In the event that a subject withdraws consent, an attempt **should** be made **at the time of consent withdrawal** to **obtain consent for** survival status.

Section 6.3 Double-blind Treatment Period, last paragraph, List Bullet 2

Formerly:

- Subjects who wish to continue in the open-label extension, will have study agent administered at the Day 364 (Week 52) visit after all Day 364 (Week 52) assessments are performed (refer to Table 6-1 below).

Modified to:

- Subjects who wish to continue in the open-label extension, will have study agent administered at the Day 364 (Week 52/**Day 0 of open-label extension**) visit after all Day 364 (Week 52) assessments are performed (refer to Table 6-1 below).

Table 6-1 Study Calendar, On treatment evaluations, Post-Treatment Follow-up Period, Study Day and Study Week, 2nd Column

Formerly:

Study Day: ~~Day 364~~ for non-completers ± 7 days

Study Week: ~~Wk 52~~

Modified to:

Study Day: **Post txt f-up** for non-completers ± 7 days

Study Week: **4 Wks post last dose**

Table 6-1 Study Calendar, On treatment evaluations, Laboratory Assessments, HIV, Hepatitis B, C: Screening

Formerly:

HIV, H~~BsAg~~,and Hepatitis C ~~antibody~~

Modified to:

HIV, H**epatitis B**, and Hepatitis C **serology**

Table 6-1 Study Calendar, On treatment evaluations
Footnotes

Deleted: (Note: subsequent footnotes have been adjusted in the table and footnotes accordingly – these changes are not shown below):

M ~~For subjects who had a positive anti-belimumab antibody response at the 8 week follow-up visit (or last study visit at which immunogenicity was assessed if 8 week follow-up visit 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 (see Section 6.8).~~

Formerly:

A The Exit (Day 364) visit will occur approximately 4 weeks after the last dose of study agent. For subjects completing all 48 weeks of treatment and continuing into the 6-month open-label extension, this visit will also serve as their 1st (ie, Day 0) visit of the 6-month open-label extension (see Table 6-2).

D Weight should be obtained prior to dosing at each visit to calculate the dose to be administered.

G Serum pregnancy test required at screening. Results of urine pregnancy test at subsequent visits, if required, must be available prior to dose. See Section 6.1

(Screening Procedures) for definition of those exempted from subsequent pregnancy testing.

N Subjects who discontinue study agent treatment at any time during the study will ~~be followed at Week 52 for survival status~~**.** In the event that a subject withdraws consent, an attempt should be made at the time of consent withdrawal to obtain consent for survival status at Week 52.

Modified to:

A The Exit (Day 364) visit will occur approximately 4 weeks after the last dose of study agent. For subjects completing all 48 weeks of treatment and continuing into the 6-month open-label extension, this visit will also serve as their 1st (ie, Day 0) visit of the 6-month open-label extension (see Table 6-2). **For subjects who discontinue study agent prior to Week 48, the Exit (Day 364) visit should be performed 4 weeks after the last administration of study agent and a follow-up visit 8 weeks after the last administration of study agent, and a survival assessment (eg, by phone contact) will take place approximately 52 weeks after the first dose of study agent (see Footnote N).**

D Weight should be obtained prior to dosing at each visit to calculate the dose to be administered. **At sites where it is impractical to use the subject's current body weight to calculate the dose, it is permissible to use the subject's body weight from the previous visit. However, the subject's body weight will be measured prior to dosing and if the previous visit weight and current visit weight vary by more than 10%, then the weight measured at the current visit must be used.**

G Serum pregnancy test required at screening. Results of urine pregnancy test at subsequent visits, if required, must be available prior to dose. See Section 6.1 (Screening Procedures) for definition of those exempted from subsequent pregnancy testing. **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 7.6).**

N Subjects who discontinue study agent treatment at any time during the study **will have a survival assessment (eg, by phone contact) approximately 52 weeks after the first dose of study agent.** In the event that a subject withdraws consent, an attempt should be made at the time of consent withdrawal to obtain consent for survival status at Week 52.

Section 6.4 6-Month Open-Label Extension, paragraph 1

Formerly:

Subjects on active drug or placebo will receive belimumab 10 mg/kg IV every 28 days for 6 months in the open-label extension.

Modified to:

Subjects on active drug or placebo will receive belimumab 10 mg/kg IV **approximately** every 28 days for 6 months in the open-label extension.

Section 6.4 6-Month Open-Label Extension, paragraph 3

Formerly:

The American College of Rheumatolog (ACR) draft guidance regarding steroid dosing and tapering in response to SLE flare is provided in Appendix 6.

Modified to:

The American College of Rheumatolog**y** (ACR) draft guidance regarding steroid dosing and tapering in response to SLE flare is provided in Appendix 6.

Table 6-1 Study Calendar, 6-month open-label extension

Formerly:

Study Day: Day 28 visit ± ~~3~~ days

Modified to:

Study Day: Day 28 visit ± **7** days

Table 6-3 Study Calendar, 6-month open-label extension
Urine pregnancy test: 8-week follow-up

Formerly:

Not listed.

Modified to:

Urine pregnancy test is marked "**X**" as required at this visit.

Table 6-1 Study Calendar, 6-month open-label extension, footnotes

Deleted: (Note: subsequent footnotes have been adjusted in the table and footnotes accordingly – these changes are not shown below):

~~f For subjects not continuing to receive belimumab post-study who had a positive anti-belimumab antibody response at the 8-week follow-up visit (or last study visit~~

~~at which immunogenicity was assessed if 8 week follow up visit 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, or upon completion and/or unblinding of the study, whichever is later.~~

Formerly:

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 Urine pregnancy test, as required, with results available prior to dosing.

d The weight at the current visit will be used for calculating the dose.

Modified to:

b **All subjects, including subjects who have discontinued study agent prior to Day 196, 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.**

c Urine pregnancy test, as required, with results available prior to dosing. **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 7.6).**

d The weight at the current visit will be used for calculating the dose. At **sites where it is impractical to use the subject's current body weight to calculate the dose, it is permissible to use the subject's body weight from the previous visit. However, the subject's body weight will be measured prior to dosing and if the previous visit weight and current visit weight vary by more than 10%, then the weight measured at the current visit must be used.**

Section 6.8 Immunogenicity (6-Month Follow-Up)

Deleted:

~~6.8 Immunogenicity (6-Month Follow-Up)~~
~~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.~~

New Section and Sub-section Added: Liver Stopping Criteria and Study Agent Restart

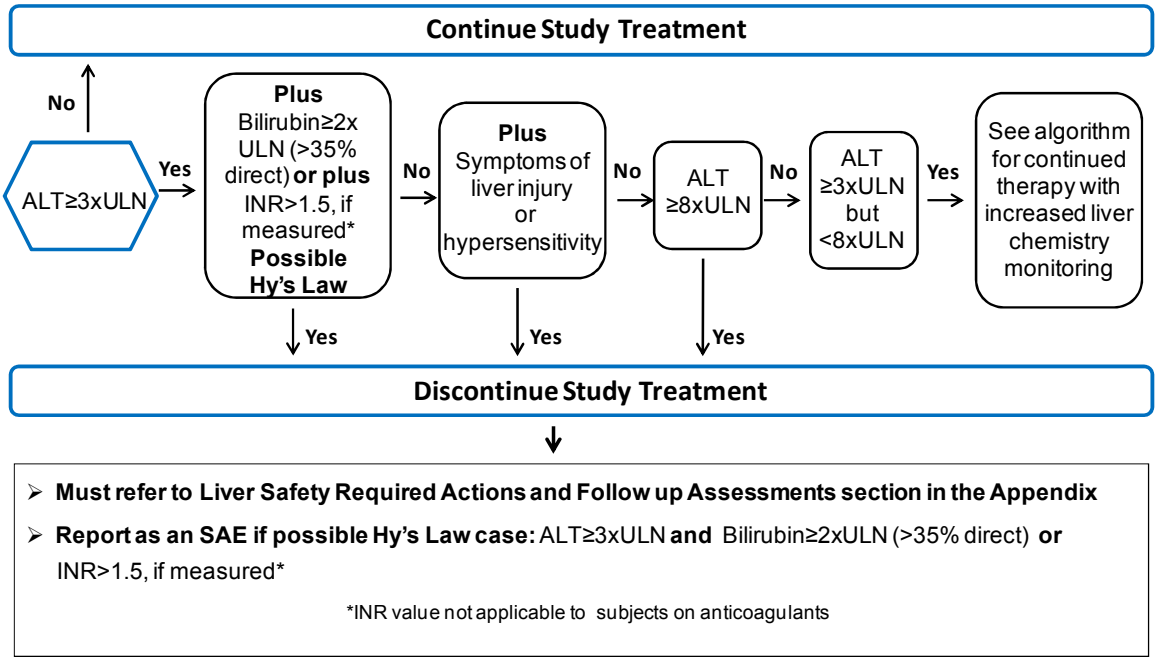
Added:

6.8.3 Liver Stopping 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).

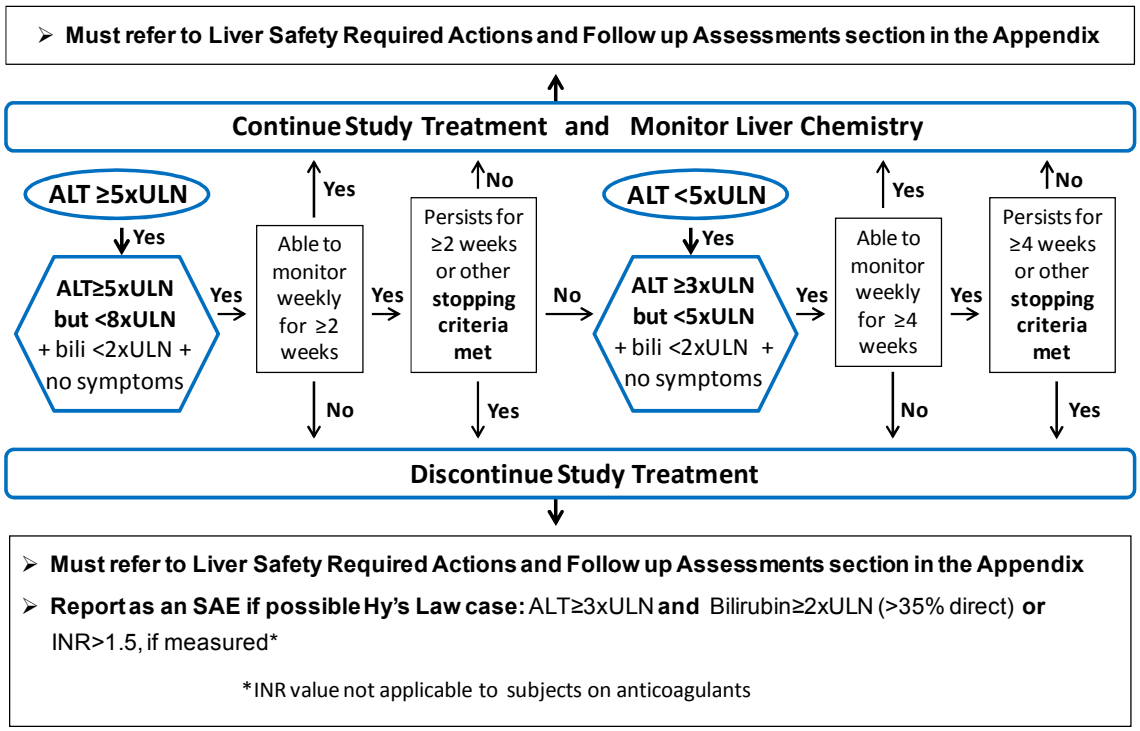
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 13.

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



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 13.

6.8.3.1 Study Agent Restart

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

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

Refer to Appendix 14 for full guidance

Section 6.9 Withdrawal of Subjects from Treatment, Bulleted List and last paragraph

Formerly:

Subjects ~~may~~ be withdrawn for any of the following reasons:

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

Subjects who discontinue treatment 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. An attempt will be made to contact all subjects ~~at Week 52~~ to determine survival status.

Modified to:

Subjects **should** be withdrawn for any of the following reasons:

- **Missing 3 or more consecutive doses of study agent.**
- Prohibited concurrent medication or therapy or prohibited dose of concurrent medication or therapy **resulting in treatment failure** (see Section 5.5).
- Unacceptable toxicity **(See Section 5.4 and Section 6.8.3)**.
- Withdrawal of consent (including use and disclosure of research-related health information).
- Pregnancy.
- **Prior to the administration of live vaccine**

- **At the discretion of the Sponsor, conditions that may warrant termination of a subject include but are not limited to safety concerns, subject significant non-compliance with protocol visits and procedures.**

Subjects who discontinue treatment 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. An attempt will be made to contact all **discontinued** subjects to determine survival status **(eg, by phone contact) approximately 52 weeks after the first dose of study agent**.

Section 6.10 Subject Unblinding, paragraph 2

Formerly:

~~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. Whenever possible, the investigator should ~~consult with the m~~edical ~~m~~onitor prior to unblinding any subject. 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.~~

Modified to:

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 **M**edical **M**onitor 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 other 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.

Section 7 Adverse Event Reporting

Added:

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

Section 7.1 Definitions

Formerly:

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 pre-existing 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.~~

Modified to:

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 (ie, 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 (eg, 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

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** hospitalization **or** prolongation of existing hospitalization

In general, hospitalization 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 hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. **Results in** disability/incapacity, **or**

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 (eg, 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 hospitalization but may jeopardize 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 hospitalization, 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.

Section 7.2 Reporting Adverse Events to the Sponsor, paragraphs 2, 3, and 4

Formerly:

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 Procedure Manual. ~~SAE Worksheets should be sent by the EDC system (if EDC functionality is available) or by facsimile to the HGS Drug Safety designee using the toll free fax number listed on the SAE Worksheet~~.

In addition, prior to study drug administration, any SAE assessed **as related** to study participation (eg, protocol mandated procedures, invasive tests) will be ~~recorded on the SAE worksheet and~~ reported as ~~described above~~ from the time a subject consents to participate in the study. ~~Pre-treatment SAEs will not be documented on the AE eCRF~~.

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 ~~definitely,~~ possibly~~, or probably~~ related to study agent must be reported to the ~~Drug Safety designee on the SAE worksheet. Post study SAEs will not be documented on the AE eCRF~~.

Modified to:

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 follow-up information** 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.

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 possibly related to study agent must be reported to the **Sponsor as outlined in the Study Procedures Manual**.

Section 7.3 Laboratory Abnormalities as Adverse Events

Formerly:

~~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).

Laboratory tests are graded according to the Adverse Event Severity Grading Tables in Appendix 12. If a particular lab test is not listed in the Appendix, the lab test should be graded as mild, moderate, severe, ~~or life-threatening~~ as specified in Section 7.7.

Modified to:

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, 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).

Laboratory tests are graded according to the Adverse Event Severity Grading Tables in Appendix 12. If a particular lab test is not listed in the Appendix, the lab test should be graded as mild, moderate, **or** severe as specified in Section 7.7.

Section 7.4 Progressive Multifocal Leukoencephalopathy

Formerly:

~~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 HGS.~~

Modified to:

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.

Section 7.6 Reporting a Pregnancy

Formerly:

~~Pregnancies must be reported to the HGS Drug Safety within 24 hours of the site becoming aware of a pregnancy in a study 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 3 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 Sections7.1and 7.2.~~

Modified to:

Any pregnancy that occurs during study participation and up to 16 weeks post dose must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to the Sponsor within 2 weeks of learning of its occurrence. The pregnancy must be followed to delivery to determine outcome

(including premature termination) and status of mother and child. To gain additional information on pregnancy outcomes, the subject will be requested to complete a 1 year infant questionnaire.

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.

Section 7.7 Investigator Evaluation of Adverse Events

Formerly:

The investigator will evaluate all adverse events with respect to seriousness (criteria listed above), severity (intensity ~~or grade~~), and causality (relationship to study agent). The criteria for seriousness 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 12. If an AE does not have Adverse Event Severity Grading in Appendix 12, 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~~

~~*Note – a severity assessment of Life-threatening is not necessarily the same as Life-threatening as a "Serious" criterion. The latter means that the event is an immediate threat to life as opposed to a potential 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 SAE worksheet is completed. The initial causality assessment may be revised as new information becomes available.~~

Modified to:

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 12) **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 (ie, 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 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.

Section 7.8 Follow-up of Adverse Events

Formerly:

~~A~~dverse 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~~.

Modified to:

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.**

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.

Section 7.9 Reporting Serious Adverse Events to Regulatory Authorities and Institutional Review Boards/Independent Ethics Committees

Formerly:

7.9 ~~**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 (eg, 7/15 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. 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).~~

~~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, as appropriate, 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~~

Modified to:

7.9 **Disease Related Events**

Disease related events (DREs) can occur in the study population regardless of belimumab exposure and are not reported as AEs or SAEs, unless judged by the investigator to be more severe than expected for the subject's condition.

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

Butterfly rash
Cutaneous lupus erythematosus
Lupus pneumonitis
Lupus vasculitis

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

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).

Section 7.10

The following section has been added:

Section 7.10 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 (eg, 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.

Section 8.3 Data Monitoring Committee (DMC)

Formerly:

Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will review unblinded safety data for this Phase 3/4 ~~program~~ on an ongoing basis until the data are locked and analyzed. The DMC will include at least 3 physicians, and a statistician, none of whom are affiliated with the sponsor. The 1st DMC data review meeting will occur after the first 100 subjects have been treated through Day 56, or within 6 months of the treatment of the 1st subject, whichever is earlier. After the initial review, the committee will review the data approximately every 6 months. ~~The DMC will monitor these trials until the data are locked and analyzed through Week 52, after which time monitoring may be assumed by an internal HGS committee.~~ Investigators 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 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~~.

Modified to:

Independent Data Monitoring Committee (**I**DMC)

An **I**ndependent Data Monitoring Committee (**I**DMC) will review unblinded safety data for this Phase 3/4 **study** on an ongoing basis until the data are locked and analyzed **through Week 52**. The **I**DMC will include at least 3 physicians, and a statistician, none of whom are affiliated with the sponsor. **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.** The 1st **I**DMC data review meeting will occur after the first 100 subjects have been treated through Day 56, or within 6 months of the treatment of the 1st subject, whichever is earlier. After the initial review, the committee will review the data approximately every 6 months. **At all times the sites and sponsor will remain blinded to treatment allocation.** Investigators **and IRBs/IECs, as appropriate,** will be notified of the outcome of each **I**DMC meeting.

The **I**DMC 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 **monthly** to the **I**DMC.

After Week 52, the monitoring may be assumed by an internal GSK/HGS committee.

Section 8.4 Sample Size Rationale

Formerly:

Approximately ~~816~~ subjects will be randomized and treated in the study, with a target of ~~544~~ subjects in the arm receiving belimumab and ~~272~~ subjects in the arm receiving

placebo. This sample size provides at least 90% power at a 5% level of significance to detect a minimum of a ~~12%~~ absolute improvement in the response rate for the belimumab group ~~(assumed rate = 56%)~~ relative to the placebo group (assumed rate = ~~44%~~) at Week 52. ~~The selection of the 12% absolute improvement is evidence-based on the observed response rate from the pooled Phase 3 data (protocols HGS1006-C1056 and C1057). The sample size calculation uses the most conservative estimate for the standard deviation in the population (ie, population SD = 50%).~~

Modified to:

Approximately **501** subjects will be randomized and treated in the study, with a target of **at least 334** subjects in the arm receiving belimumab and **167** subjects in the arm receiving placebo. This sample size provides at least 90% power at a 5% level of significance to detect a minimum of a **15.55%** absolute improvement in the SRI response rate with the modified SLEDAI-2K scoring for proteinuria for the 10 mg/kg belimumab group relative to the placebo group (assumed rate =**43.95%**) at Week 52. **This sample size is also sufficient to provide approximately 80% power at a 5% level of significance to detect a minimum of a 13.4% absolute improvement in the SRI response rate with the SELENA SLEDAI scoring for proteinuria for the 10 mg/kg belimumab group relative to the placebo group (assumed rate = 44.8%).**

The selection of the assumed treatment differences is based on the observed SRI data from studies BEL112341 (HGS1006-C1115/BLISS SC) and BEL113750 (Northeast Asia), which are two efficacy studies that concluded in 2015 and 2016, respectively, and have nearly identical eligibility criteria to study HGS1006-C1112 including requiring a screening SS score ≥8. SRI results, calculated using the SS results and calculated using a modification to the proteinuria scoring based on SLEDAI-2K rules, are shown in Table 8-1.

Table 8-1 SRI Results From Studies BEL112341 and BEL113750

	SRI *Calculated Using the SS Results as Collected*			SRI *Calculated Using SS Results with the Modified SLEDAI-2K Proteinuria Scoring*		
Dataset	**Placebo**	**Belimumab**	**Δ**	**Placebo**	**Belimumab**	**Δ**
BEL112341*	**48.4%**	**61.4%**	**12.98%**	**46.6%**	**61.7%**	**15.14%**
BEL113750**	**40.1%**	**54.3%**	**14.17%**	**40.2%**	**56.3%**	**16.16%**
Pooled BEL112341 and BEL113750	**44.8% (222/496)**	**58.2% (582/1000)**	**13.44%**	**43.95% (218/496)**	**59.50% (595/1000)**	**15.55%**

*** Inclusion criterion SS≥8, 200 mg SC dose used.**
****Inclusion criterion SS≥8, 10 mg/kg IV dose used.**

All sample size calculations were performed using Power Analysis and Sample Size software (PASS 2012).

Section 8.5.4 Other Efficacy Endpoints, Endpoints Supporting Primary Efficacy Endpoint, #2 and Note

Formerly:

Endpoints Supporting Primary Efficacy Endpoint:

2. Percent of subjects with a ≥ 4 point reduction from baseline in SELENA SLEDAI at Week 52 and by visit.

The SRI 5-8 are defined identically to the SRI except for using higher thresholds of improvement for SELENA SLEDAI reduction for a patient to be declared a responder (eg, SELENA SLEDAI ≥ 5 point reduction for SRI5).

Modified to:

Endpoints Supporting Primary Efficacy Endpoint **(SRI where SELENA SLEDAI score is modified to use the SLEDAI-2K scoring for proteinuria)**:

2. Percent of subjects with a ≥ 4 point reduction from baseline in SELENA SLEDAI **(modified to use the SLEDAI-2K scoring for proteinuria)** at Week 52 and by visit.

The SRI 5-8 are defined identically to the SRI except for using higher thresholds of improvement for SELENA SLEDAI **(modified to use the SLEDAI-2K scoring for proteinuria)** reduction for a patient to be declared a responder (eg, SELENA SLEDAI ≥ 5 point reduction for SRI5).

Section 8.5.4 Other Efficacy Endpoints, Disease activity, #2

Formerly:

2. Mean percent change and mean change in SELENA SLEDAI score by visit.

Modified to:

2. Mean percent change and mean change in SELENA SLEDAI score **with the modified SLEDAI-2K scoring for proteinuria** by visit.

Section 8.5.4 Other Efficacy Endpoints, Organ Specific, #1 and #2

Formerly:

1. Percent of subjects with organ improvement by SELENA SLEDAI by visit.

2. Percent of subjects with organ worsening by SELENA SLEDAI by visit.

Modified to:

1. Percent of subjects with organ improvement by SELENA SLEDAI by visit. **The renal domain will use the SLEDAI-2K proteinuria scoring as the primary method with the SELENA SLEDAI proteinuria scoring as a sensitivity analysis.**

2. Percent of subjects with organ worsening by SELENA SLEDAI by visit. **The renal domain will use the SLEDAI-2K proteinuria scoring as the primary method with the SELENA SLEDAI proteinuria scoring as a sensitivity analysis.**

Section 8.5.4 Other Efficacy Endpoints, SFI Flare

Formerly:

SFI Flare:

Modified to:

SFI Flare **(SFI where SELENA SLEDAI score is modified to use the SLEDAI-2K scoring for proteinuria)**:

Section 8.5.4 Other Efficacy Endpoints, Biological Markers, footnote

Formerly:

*Anti-dsDNA will be collected monthly throughout the study for SELENA SLEDAI scoring. ANA will be collected at screening and baseline only. Other autoantibodies will be collected from all patients at baseline, then at regular intervals in patients positive at baseline.

Modified to:

*Anti-dsDNA will be collected monthly throughout the study for SELENA SLEDAI scoring **modified to use the SLEDAI-2K scoring for proteinuria**. ANA will be collected at screening and baseline only. Other autoantibodies will be collected from all patients at baseline, then at regular intervals in patients positive at baseline.

Section 8.5.5 Secondary Efficacy Analyses

Added:

The SRI response rate with the SELENA SLEDAI scoring for proteinuria at Week 52 will be compared between the belimumab treatment group and the placebo group using the same analysis methods as described for the primary endpoint in Section 8.5.2.

Section 11 References

Added:

Cervera R, Khamashta MA, Font J, et al. Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period: A Comparison of Early and Late Manifestations in a Cohort of 1,000 Patients. Medicine 2003;82:299-308.

Cervera R, Khamasta MA, Hughes GRV. The Euro-Lupus project: epidemiology of systemic lupus erythematosus in Europe. Lupus. 2009;18:869-874.

Cervera R. Systemic Lupus Erthematosus in Europe at the change of the millennium: Lessons from the "Euro-Lupus Project". Autoimmunity Reviews. 2006;5:180-186.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of acetaminophen-adduct in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos 2009; 37:1779-1784.

Karassa FB, Magliano M, and Isenberg DA. Suicide attempts in patients with systemic lupus erythematosus. Ann Rheum Dis. 2003;62(1):58-60.

Section Appendix 1, Rows 4, 5, and 9

Formerly:

4. Oral ulcers	Oral or nasopharyngeal ulceration usually painless.
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints characterized by tenderness.
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).

Modified to:

4. Oral ulcers	Oral or nasopharyngeal ulceration usually painless**, observed by physician**.
5. Nonerosive Arthritis	Nonerosive arthritis involving 2 or more peripheral joints characterized by tenderness**, swelling, or effusion**.

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).

Appendix 10

Added:

Other Screening Labs

HBsAg and HB Core antibody

Liver event follow-up assessments:

Hepatitis A IgM antibody
HBsAg and HB Core antibody (IgM)
Hepatitis C RNA
Cytomegalovirus IgM antibody
Epstein-Barr viral capsid antigen IgM antibody
Hepatitis E IgM antibody
CPK
Anti-smooth muscle antibody
Type 1 anti-liver kidney microsomal antibodies

Appendix 11, Pharmacogenetic Research. Study Assessments and Procedures

Formerly:

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.

Modified to:

In addition to any blood samples drawn for the clinical study, a whole blood sample (~**6 to 8** mL) will be collected for the PGx research at baseline.

New Appendix 13

Added:

Appendix 13 Liver Safety Required Actions and Follow up Assessments

Phase III-IV 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).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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

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

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5] • Blood sample for pharmacokinetic (PK) analysis, obtained within approximately 1 to 2 weeks after the liver event[6] • Serum creatine phosphokinase (CPK) and

study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 14) • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • 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 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	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.

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).
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody.
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for 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 study reference manual.

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss 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 • 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.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.
Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

New Appendix 14

Added:

Appendix 14 Liver Safety – Study Treatment Restart Guidelines

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

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments,

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

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (eg, biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

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, possible study treatment-induced liver injury) or study treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) 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.