

TITLE PAGE

Division: Worldwide Development

Information Type: Protocol Amendment

Title:	An Open-label, Non-randomized, 52-Week Study to Evaluate Treatment Holidays and Rebound Phenomenon After Treatment With Belimumab 10 mg/kg in Systemic Lupus Erythematosus Subjects
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Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2012N154810_00	2013-AUG-22	Original
2012N154810_01	2013-OCT-04	Amendment No. 1
<p>China Specific Protocol Amendment.</p> <p>Addition of description to title page to clarify amendment 01 is China specific.</p> <p>Modification of Protocol Summary study design paragraph to clarify China subject recruitment.</p> <p>Modification of Section 3.1 Investigational Plan, Study Design, Study Schematic to clarify China subjects from the open-label period of BEL113750 can be recruited.</p> <p>Modification of Section 3.1 Investigational Plan, Study Design, description of three subject groups.</p> <p>Modification of Section 3.2 Discussion of Design to include recruitment of China subjects from open-label BEL113750.</p> <p>Modification of Section 4.2 Inclusion Criteria for China subjects in the open-label period of BEL113750.</p> <p>Modification of Section 4.3 Exclusion Criteria for China subjects in the open-label period of BEL113750.</p> <p>Modification of Section 5.1 Investigational Product and Other Study Treatment for China subjects in the open-label period of BEL113750.</p> <p>Modification of Section 6, Time and Events Table footnotes for China subjects in the open-label period of BEL113750.</p> <p>Modification of Section 6.1.2 Secondary Endpoints for China subjects in the open-label period of BEL113750.</p> <p>Modification of Section 6.2 Critical Baseline Assessments for China subjects in the open-label period of BEL113750.</p> <p>Modification of Section 6.3.1.1 SELENA SLEDAI Score for China subjects in the open-label period of BEL113750.</p> <p>Addition of Section 6.4.1.1 for Additional Hepatitis B Monitoring for consistency with the parent/feeder China specific BEL113750 protocol amendment 04 hepatitis B changes.</p> <p>Modification of Section 6.7 Pharmacogenetic Research clarifying PGx sampling not needed from China subjects from the BEL113750 study.</p> <p>Modification of Appendix 11.5 Clinical Laboratory Tests for consistency with the parent/feeder China specific BEL113750 protocol amendment 04.</p> <p>Appendix 8 added, providing detailed changes to the protocol.</p>		

2012N154810_02	2014-JAN-14	Amendment No. 2
<p>Updating of Progressive Multifocal Leuko-encephalopathy (PML) wording to reflect new information received by the Sponsor; global administrative changes regarding study phase mentioned in the protocol.</p> <p>Modification of title regarding the study phase.</p> <p>Addition of description to title page to clarify that protocol amendment 02 is a global protocol amendment.</p> <p>Modification of the Protocol Summary of the Study Design section for sponsor administrative change of study phase.</p> <p>Modification of Section 3.1 for sponsor administrative change of study phase.</p> <p>Updating of Section 6.4.13.1 Progressive Multifocal Leukoencephalopathy (PML).</p> <p>Updating of Appendix 5 Clinical Laboratory Tests.</p> <p>Updating of Appendix 7 Country Specific Requirements to include China Specific Protocol Amendment 01 changes in this protocol amendment 02.</p> <p>Updating of Appendix 8 Protocol Changes.</p>		
2012N154810_03	2014-APR-01	Amendment No. 3
<p>Sponsor administrative change affecting the Interactive Voice Response System (IVRS).</p> <p>Update sponsor serious adverse event (SAE) contact information on the Sponsor Information Page.</p> <p>Correction of typographical error in Section 5.1 Investigational Product and Reference Therapy regarding the 1 hour infusion time.</p> <p>Modification of Section 5.2 Treatment Assignment regarding the Interactive Voice Response System (IVRS) due to a sponsor administrative change.</p> <p>Clarification of Section 5.5.1 Permitted Medications and Non-Drug Therapies regarding subjects receiving live vaccines.</p> <p>Clarification of Section 6 Study Assessments and Procedures, Time and Events Table (Year 1) for informed consent signing footnote 4.</p> <p>Clarification of Section 6 Study Assessments and Procedures, Time and Events Table (Year 1) for PK sampling footnote 12 for Long-term discontinuation subjects withdrawing from the study.</p> <p>Clarification of Section 6.2 Critical Baseline Assessments for signing the informed consent form.</p> <p>Clarification of Section 6.6 Pharmacokinetics for PK sampling for Long-term discontinuation subjects withdrawing from the study.</p> <p>Clarification of Section 9.2 Regulatory and Ethical Considerations, Including the Informed Consent Process, for signing the informed consent form.</p>		

2012N154810_04	2015-AUG-31	Amendment No. 4
<p>Updates to SPONSOR INFORMATION PAGE for the Primary Medical Monitor and Backup Medical Monitor telephone numbers, and Case Management Group email address and fax number. The Regulatory Agency Identifying Number was also added as United States clinical sites joined this study.</p> <p>Modification of Section 3.1 Study Design describing when the maintenance phase of BEL116027 may end.</p> <p>Modification of Section 5.6 Treatment after the End of the Study describing when the maintenance phase of BEL116027 may end.</p> <p>Modification of Section 6 Study Assessments and Procedures, Table 2, Time and Events Table (Year 1), footnote 3 to correct typographical error, as no switching between the three groups is allowed.</p> <p>Modification of Section 6.4.1 Liver chemistry stopping and follow up criteria.</p> <p>Addition of Section 6.4.1.1 Study Treatment Restart, as relating to liver stopping criteria.</p> <p>Modification of Section 8.1.6 Interim Analysis to correct typographical errors.</p> <p>Modification of Section 9.5 Study and Site Closure describing when the maintenance phase of BEL116027 may end.</p> <p>Addition of Le Gal 2005 reference to Section 10 References, as Le Gal 2005 reference added to liver chemistry stopping and follow up criteria section updates.</p> <p>Modification of Section 11.7 Appendix 7: Country Specific Requirements describing when the maintenance phase of BEL116027 may end.</p> <p>Updated Phase III-IV Liver Safety Algorithms in Section 11.3, Appendix 3.</p>		
2012N154810_05	2015-DEC-03	Amendment No. 5
<p>Modification of Section 6, Study Assessments and Procedures, Table 2, Time and Events Table (Year 1) to clarify that the PK assay is needed as part of immunogenicity testing.</p> <p>Modification of Section 6.4.7 Time Period and Frequency of Detecting AEs and SAEs to clarify SAE reporting for China sites.</p> <p>Modification of Section 6.4.16 Immunogenicity to clarify that an attempt will be made to determine the amount of belimumab (PK) present in immunogenicity samples with confirmed anti-drug binding antibodies (ADA).</p> <p>Modification of Section 6.4.16 Immunogenicity as neutralizing antibody testing will not be performed in China.</p> <p>Modification of Section 6.6 Pharmacokinetics to clarify that the PK assay is needed as</p>		

part of immunogenicity testing.

Modification of Section 11.5, Appendix 5: Clinical Laboratory Tests updated to include the additional labs mentioned in Section 6.4.1 liver Chemistry stopping and follow up criteria which was updated in the previous amendment.

2012N154810_06

2017-SEP-12

Amendment No. 6

Updates to Sponsor Information Page for Backup Medical Monitor.

Modification of Section 3.1 Study Design, Section 3.2 Discussion of Design, Section 4, Number of Subjects, and Section 8 Data Analysis and Statistical Considerations updated for change in sample size as agreed upon with the European Medicines Agency (EMA).

Modification of Section 3.1 Study Design to provide clarification.

Modification of Protocol Summary, Section 3.1 Study Design, and Section 3.2 Discussion of Design to provide clarification on Appendix 11.7, recruitment of China subjects from open-label BEL113750.

Modification of Section 4.4 Withdrawal Criteria to provide clarification.

Modification of Section 6 Study Assessments and Procedures to provide clarification.

Modification of Section 6.1.4. Definitions of SLE Flares Used in This Study to update definition of renal flare by removing hematuria criteria.

Updates to Appendix 7 Country Specific Requirements to include corresponding updates from protocol amendment 06 to the China Specific Protocol Amendment 01.

2012N154810_06

CONFIDENTIAL

BEL116027

SPONSOR SIGNATORY

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12 Sep 2017

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SPONSOR INFORMATION PAGE

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number BEL116027

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	
Investigator Signature	Date

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LIST OF ABBREVIATIONS

µmol	Micromoles
aCL	Anticardiolipin
ACR	American College of Rheumatology
ADA	Anti-drug Antibodies
AE	Adverse Event
ALT	Alanine Aminotransferase
ANA	Anti-nuclear Antibody
Anti-IL-6	Anti-Interleukin-6
Anti-TNF	Anti-Tumour Necrosis Factor
AST	Aspartate Aminotransferase
BLyS	B Lymphocyte Stimulator
CBC	Complete Blood Count
CNS	Central Nervous System
CPK	Creatinine Phosphokinase
CrCL	Creatinine Clearance
DAS	Disease Activity Scales
dL	Decilitre
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic Acid
dsDNA	Double Stranded Deoxyribonucleic Acid
ECL	Electrochemiluminescence
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
g	Gram
GFR	Glomerular Filtration Rate
GSK	GlaxoSmithKline
HBV	Hepatitis B Virus Quantitative DNA PCR
HGS	Human Genome Sciences, Inc
hpf	High Power Field
HPLC	High Pressure Liquid Chromatography
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine Device
IUS	Intrauterine System
IV	Intravenous
IVIG	Intravenous Immunoglobulins
IVRS	Interactive voice response system
kg	Kilograms
L	Litre

LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Affairs
mg	Milligrams
mL	Millilitre
MMF	Mycophenolate
MSD	Meso Scale Discovery
MSDS	Materials Safety Data Sheet
NSAIDs	Non-steroidal Anti-inflammatory Drugs
NWHIC	National Women's Health Information Center
OL	Open-label
OMHRC	Office of Minority Health Resource Center
PCR	Polymerase Chain Reaction
PGA	Physician's Global Assessment
PK	Pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
PT	Prothrombin Time
PTT	Partial thromboplastin Time
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SELENA	Safety of Estrogen in Lupus National Assessment
SFI	SLE Flare Index
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SOC	Standard of Care
SPM	Study Procedures Manual
SS	SELENA SLEDAI Score
SWFI	Sterile Water for Injection
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analogue Scale

Trademark Information

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PROTOCOL SUMMARY

Rationale

Belimumab is currently approved as a treatment for SLE but there is no current efficacy or safety data on the effects of temporary discontinuation of belimumab therapy in subjects with stable low disease activity and subsequent reintroduction of belimumab therapy (so-called ‘treatment holidays’) or data on rebound phenomenon. This study is intended to provide data on treatment holidays and rebound phenomenon of belimumab therapy in SLE and to fulfil a post-marketing commitment made to the European Medicines Agency (EMA).

This study will assess the effect of a 24-week withdrawal followed by a 28-week reintroduction of belimumab 10 mg/kg plus standard of care on immunogenicity, markers of biological activity, efficacy, and safety in subjects with stable low SLE disease activity. In addition, this study will assess rebound phenomenon in subjects with any disease level of SLE who have permanently withdrawn from further belimumab treatment.

Objectives

Primary Objective

Characterize the efficacy of a 24-week withdrawal followed by a 28-week reintroduction of intravenous belimumab therapy compared with uninterrupted intravenous belimumab therapy for 52 weeks in subjects with low SLE disease activity receiving belimumab 10 mg/kg plus standard of care, as measured by time to first flare.

Secondary Objectives

- Evaluate the rate of any flare.
- Assess safety, SLE disease activity, immunogenicity, markers of autoimmune response (e.g., immunoglobulins, complement), and changes in corticosteroid use.

Study Design

A phase IIIB, multi-centre, open-label, non-randomized, efficacy and safety study (including potential rebound) of:

- the effect of temporary discontinuation of belimumab 10 mg/kg therapy for 24 weeks and reintroduction of belimumab 10 mg/kg therapy for 28 weeks plus standard of care (referred to as ‘treatment holiday’) in subjects with low SLE disease activity.
- rebound phenomenon in subjects who have discontinued belimumab therapy (stratified by SLE disease activity, SELENA SLEDAI score ≤ 3 or SELENA SLEDAI score >3).

The study consists of a screening phase of up to 30 days, a 52-week treatment/observation phase with an escape option, a maintenance phase, and a follow-up phase. The study consists of a treatment holiday group, a control group, and a long-term discontinuation group. All 3 subject groups will be recruited from the BEL114333 continuation study of belimumab in SLE and as described in Appendix 11.7, from the open-label (OL) period BEL113750 for China subjects. Additionally, subjects in the long-term discontinuation group will also be recruited from the HGS1006-C1066 and LBSL99 continuation studies of belimumab in SLE. All subjects will be assessed every 4 weeks for 52 weeks. After 52 weeks, eligible subjects in the treatment holiday and control groups have the option to continue receiving belimumab therapy in the maintenance phase of this study. Two follow-up visits are scheduled for subjects in the treatment holiday and control groups who are prematurely withdrawn from the study. Subject completion for subjects in the treatment holiday group is defined as completion of the 24-week treatment holiday period plus the belimumab re-introduction treatment period to Week 52. Subject completion for subjects in the control and long-term discontinuation groups is defined as completion of all visits to Week 52.

Study Endpoints/Assessments

Efficacy will be assessed from, SELENA SLEDAI (SS) score, SLE flare index Physician's Global Assessment (PGA) and SLICC/ACR damage index. The primary efficacy endpoint is time to any SLE Flare Index flare.

The safety assessments are adverse events (AEs) (including infusion-related and hypersensitivity reactions, infections and malignancies), haematological and clinical chemistry parameters, urinalysis, B cell markers, immunogenicity, vital signs (including weight), and physical examinations.

1. INTRODUCTION

1.1. Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterised by autoantibody production and abnormal B lymphocyte function [Pisetsky, 2001]. This disease is more common in women (~90% of patients) than men [NWHIC, 2003] and prevalence varies with race [OMHRC, 2001; NWHIC, 2003]. SLE can lead to arthritis, kidney failure, heart and lung inflammation, and central nervous system (CNS) changes. 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

A clinical diagnosis of SLE includes features that are thought to involve dysregulation of B lymphocytes [Lioussis, 1996; Lipsky, 2001]. The B lymphocyte stimulator (BLyS) protein is a potent co-stimulator of B lymphocytes and elevated levels of BLyS are observed in autoimmune diseases in humans and animal models [Cheema, 2001; Gross, 2001; Khare, 1999; Mackay, 1999; Moore, 1999; Zhang, 2001; Carter, 2003]. In SLE, the elevation of BLyS may contribute to the persistence of B cell subsets that produce pathogenic autoantibodies or promote inflammation that would otherwise be subject to down regulation. Thus a therapeutic strategy which involves an antagonist to BLyS, to reduce B lymphocyte stimulation, reducing autoantibody production, may have therapeutic benefit in SLE.

Belimumab is currently approved in the United States, Canada and Europe for the treatment of SLE. Belimumab is a B lymphocyte stimulator (BLyS)-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptor 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. Further information on the risk benefit of belimumab is provided in the Investigator Brochure (IB) and in the belimumab product label.

1.2. Rationale

Belimumab is currently approved as a treatment for SLE but there is no current efficacy or safety data on the effects of temporary discontinuation of belimumab therapy in subjects with stable low disease activity and subsequent reintroduction of belimumab therapy (so-called ‘treatment holidays’) or data on rebound phenomenon. This study is intended to provide data on treatment holidays and potential rebound phenomenon of belimumab therapy in SLE and to fulfil a post-marketing commitment made to the European Medicines Agency (EMA).

This study will assess the effect of a 24-week withdrawal followed by a 28-week reintroduction of belimumab 10 mg/kg plus standard of care on immunogenicity, markers of biological activity, efficacy, and safety in subjects with stable low SLE disease activity. In addition, this study will assess rebound phenomenon in subjects with any disease level of SLE who have permanently withdrawn from further belimumab treatment.

2. OBJECTIVE(S)

2.1. Primary Objective

Characterize the efficacy of a 24-week withdrawal followed by a 28-week reintroduction of intravenous belimumab therapy compared with uninterrupted intravenous belimumab therapy for 52 weeks in subjects with low SLE disease activity receiving belimumab 10 mg/kg plus standard of care, as measured by time to first flare.

2.2. Secondary Objectives

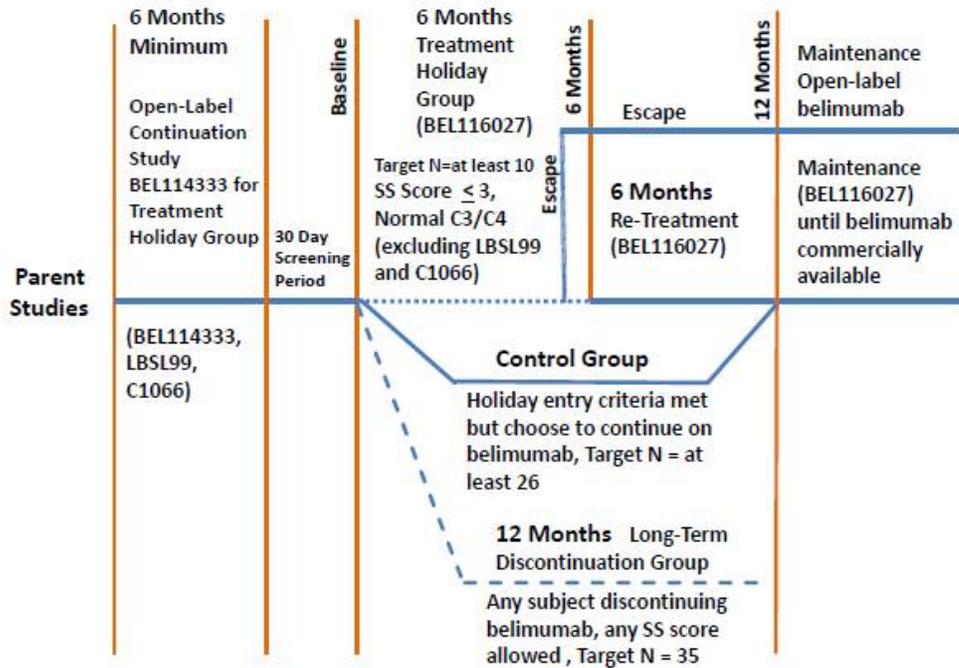
- Evaluate the rate of any flare.
- Assess safety, SLE disease activity, immunogenicity, markers of autoimmune response (e.g., immunoglobulins, complement), and changes in corticosteroid use.

3. INVESTIGATIONAL PLAN

3.1. Study Design

A phase IIIB, multi-centre, open-label, non-randomized, efficacy and safety study (including potential rebound) of:

- the effect of temporary discontinuation of belimumab 10 mg/kg therapy for 24 weeks and reintroduction of belimumab 10 mg/kg therapy for 28 weeks plus standard of care (referred to as ‘treatment holiday’) in subjects with low SLE disease activity ([Figure 1](#)).
- rebound phenomenon in subjects who have discontinued belimumab therapy ([Figure 1](#)).

Figure 1 Study Schematic

Subjects will be recruited from 3 open-label continuation studies of belimumab in SLE. See Appendix 11.7 for recruitment from the open-label (OL) period BEL113750 for China subjects. This study will comprise 3 distinct groups of subjects as outlined below:

- Treatment Holiday group:** This group will be used to assess the effect of temporary discontinuation (including rebound phenomenon) and re-introduction of belimumab 10 mg/kg therapy. These subjects will be recruited from the BEL114333 belimumab continuation study in subjects with SLE. Subjects will have been treated with belimumab for at least 6 months and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal. The target enrolment for this group is at least 10 subjects.
- Treatment Control group:** This group will serve as a control to the treatment holiday group. These subjects will be recruited from the BEL114333 belimumab continuation study in subjects with SLE. Subjects will have been treated with belimumab for at least 6 months and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal but will continue their current treatment with belimumab 10 mg/kg. The target enrolment for this group is at least 26 subjects.
- Long-term Discontinuation group:** This group will also be used to assess rebound phenomenon in SLE subjects who have discontinued therapy with belimumab 10 mg/kg and are expected to remain off belimumab therapy for at least 12 months but remain on standard of care therapy. These subjects will be recruited from 3

belimumab open-label continuation studies in subjects with SLE (BEL114333; HGS1006-C1066; LBSL99). Subjects will have been treated with belimumab for at least 6 months in one of these continuation studies but will have withdrawn from belimumab therapy for no longer than 8 weeks prior to entry into this study. These subjects may have any level of SLE disease activity. The target enrolment for this group is 35 subjects.

The study consists of a screening phase of up to 30 days, a 52-week treatment/observation phase with an escape option, a maintenance phase, and a follow-up phase. The screening phase will allow an assessment of the SELENA SLEDAI score and complement (C3 and C4) levels as part of the eligibility criteria for subjects in the treatment holiday and control groups. All subjects will attend clinic visits for efficacy and safety assessments every 4 weeks for 52 weeks. At the end of the 52 week period, subjects in the treatment holiday and control groups will have the option to continue belimumab therapy in the maintenance phase of this study only if belimumab is not commercially available in a subject's country of participation. This maintenance phase will last until such time as belimumab becomes commercially available in a subject's country of participation, or the Sponsor discontinues the maintenance phase of the study for China subjects with the provision for China subjects to elect to participate in a different protocol to continue to receive belimumab, or the Sponsor decides to terminate the study. Safety reporting will be as specified in the protocol the subject participates in.

A 16-week follow-up visit will be scheduled for subjects in the treatment holiday and control groups after the withdrawal visit or the last dose of belimumab as appropriate. Additionally, a 6 month follow-up visit is required for those subjects in the treatment holiday or control groups.

Subjects in the treatment holiday group may re-start belimumab therapy prior to Week 24 in the event of a severe SLE flare as per the SLE flare index ([Appendix 1](#)). These subjects will then enter the maintenance part of this study by the escape option for ongoing belimumab treatment.

Subject completion for subjects in the treatment holiday group is defined as completion of the 24-week treatment holiday period plus the belimumab re-introduction treatment period to Week 52. Subject completion for subjects in the control and long-term discontinuation groups is defined as completion of all visits to Week 52.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.2. Discussion of Design

This study proposes to recruit subjects from ongoing open-label continuation studies of belimumab in SLE subjects in order to obtain an eligible population in the shortest timeframe. There are 3 continuation studies of belimumab suitable for recruitment of subjects required for this study:

- **BEL114333:** A Phase III open-label continuation of parent study BEL113750, which is an ongoing Phase III, double-blind, placebo-controlled study of belimumab in SLE subjects conducted in Japan, South Korea and China (for China see Appendix 11.7 for country-specific requirements regarding recruitment from the open-label period of BEL113750).
- **HGS1006-C1066:** An ongoing Phase III, open-label continuation study of parent study HGS1006-C1056 (BLISS 76), which enrolled and treated 268 SLE subjects with belimumab conducted in the United States
- **LBSL99:** An ongoing Phase II, open-label continuation study of parent study LBSL02, which enrolled and treated 296 SLE subjects with belimumab conducted in the United States and Canada.

Subjects eligible for inclusion in the treatment holiday group will have been treated with belimumab for at least 6 months in BEL114333 and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal.

Subjects eligible for inclusion in the control group will have been treated with belimumab for at least 6 months in BEL114333 and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal but elect to continue their current treatment with belimumab 10 mg/kg.

Subjects eligible for inclusion in the long-term discontinuation group may have any level of SLE disease activity; will have been treated with belimumab for at least 6 months in any of the 3 continuation studies mentioned above; have discontinued belimumab therapy for no longer than 8 weeks prior to entry into this study and intend to remain off belimumab treatment for the 12 months of this study but to remain on standard of care therapy.

Subjects eligible for inclusion in the treatment holiday group will **not** be recruited from the long-term continuation studies LBSL99 or HGS1006-C1066, due to regulatory commitments for completing 10 years and 5 years on treatment, respectively. However, subjects who discontinue belimumab treatment in studies LBSL99 or HGS1006-C1066 can be recruited into the long-term discontinuation group in the present study.

For subjects entering the study, a minimum of 6 months previous participation in an open-label continuation study will provide subjects initially randomized to placebo in parent studies with the opportunity to reach sufficient biological activity to achieve a belimumab pharmacological and/or clinical response.

The target sample size of at least 10 subjects in the treatment holiday group and at least 26 subjects in the control group is based on estimates of subject eligibility and number of subjects from continuation study BEL114333 anticipated to provide consent to participate in this study. The target sample size of 35 subjects for the long-term discontinuation group is based on practical considerations of numbers of subjects anticipated to drop-out and not on statistical considerations.

Enrolment of subjects from the 3 belimumab continuation studies into the long-term discontinuation group will remain open while recruitment to the treatment holiday and control groups is ongoing or until 36 months have elapsed since study start. A target sample size of 35 subjects in the long-term discontinuation group is anticipated.

Because this study is non-randomized, subjects and investigators from study BEL114333 will jointly decide upon which of the three groups to enrol into. Subjects recruited from the HGS1006-C1066 and the LBSL99 studies may only choose to enter the long-term discontinuation group, as they elect to no longer receive further belimumab therapy.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

The target sample size for subjects in the treatment holiday group is at least 10 subjects and in the control group, at least 26 subjects. Each group will end recruitment when their target sample size is reached. Enrolment in this study will close when the target number of subjects in the treatment holiday and control groups has been achieved or 36 months after study start, whichever comes first. As many subjects as possible will be enrolled in the long-term discontinuation group while recruitment to the treatment holiday and control groups is ongoing and will cease when recruitment to the treatment holiday and control groups is closed or until 36 months have elapsed since study start. A target sample size of 35 subjects in the long-term discontinuation group is anticipated.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the belimumab IB/IB supplement(s) and belimumab product label.

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in **all 3 subject groups** in the study must meet all of the following criteria:

1. **Belimumab therapy:** Received a minimum of 6 months therapy with belimumab 10 mg/kg in the continuation study BEL114333. Subjects in the long-term discontinuation group may additionally be recruited from continuation studies HGS1006-C1066 or LBSL99.

2. **Age:** 18 years of age at the Day 0 visit.
3. **Females:** A non-pregnant, non-lactating female subject is eligible to enter the study if at least one of the following conditions apply:
 - Of non-childbearing potential (i.e., women who had a hysterectomy, are postmenopausal which is defined as 1 year without menses, have both ovaries surgically removed or have current documented female sterilization procedure); or
 - Of childbearing potential (i.e., 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 urine pregnancy test at Day 0, and agree to one of the following:
 - Complete abstinence from penile-vaginal intercourse, when this is the female's preferred and usual lifestyle, for the duration of the study for subjects in the long-term discontinuation group or until 16 weeks after the last dose of belimumab for subjects in the treatment holiday and control groups; or
 - Consistent and correct use of one of the following acceptable methods of birth control for the duration of the study for subjects in the long-term discontinuation group or until 16 weeks after the last dose of belimumab for subjects in the treatment holiday and control groups:
 - Implants of etonogestrel or levonorgestrel;
 - Estrogenic vaginal ring
 - Injectable progesterone;
 - Any intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year;
 - Oral contraceptives (either combined or progesterone only);
 - Double barrier method with vaginal spermicidal agent: Condom and an occlusive cap (cervical cap/vault or diaphragm) with a vaginal spermicidal agent (foam/gel/film/cream/suppository);
 - Percutaneous 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 (e.g., barrier method).

4. **Informed consent:** Able to provide written informed consent to participate.

Additional eligibility criteria for subject enrolment in the **treatment holiday and control groups** in the study:

1. **SLE:** achieve the required minimal disease activity criteria defined as SELENA SLEDAI score ≤ 3 after a minimum of 6 months of belimumab therapy (see [Appendix 1](#) for SELENA SLEDAI).
2. **SLE Treatment:** Are on a stable SLE treatment regimen consisting of any of the following medications (alone or in combination) during the 30 day screening period prior to Day 0:
 - Corticosteroids (prednisone or prednisone equivalent)
 - Other immunosuppressive or immunomodulatory agents including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), mizoribine, calcineurin inhibitors (e.g., tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine, or thalidomide.
 - Anti-malarials (e.g., hydroxychloroquine, chloroquine, quinacrine).
 - Non-steroidal anti-inflammatory drugs (NSAIDs), including sulfasalazine.
3. **Complement:** C3 and C4 complement levels at or above the lower limit of normal of the central laboratory reference range.

Additional eligibility criteria for subject enrolment in the **control group** in the study:

1. **Belimumab therapy:** Agree to continue receiving 10mg/kg belimumab intravenous infusions every 4 weeks. Subjects must be able to receive the first dose of belimumab in **this study** 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in their **previous** continuation study.

Additional eligibility criteria for subject enrolment in the **long-term discontinuation group** in the study:

1. **Continuation studies:** Voluntarily withdrawn from continuation studies BEL114333, HGS1006-C1066, or LBSL99 and have withdrawn from belimumab therapy for no longer than 8 weeks prior to entry into this study.

Note: investigators may stop, start, and/or change SLE medications and dosages as deemed necessary; yet long-term discontinuation subjects will remain on local standard of care SLE treatment therapy as determined by the physician during the study, or will need to be withdrawn.

4.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in **any of the 3 subject groups** in the study:

1. **Undue risk:** Have developed clinical evidence of significant, unstable or uncontrolled, acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases), or experienced an adverse event (AE) in the belimumab continuation studies BEL114333, HGS1006-C1066, or LBSL99 studies that could, in the opinion of the principal investigator, put the subject at undue risk.
2. **Subject suitability:** Have developed any other medical diseases (e.g., cardiopulmonary), laboratory abnormalities, or conditions (e.g., poor venous access) that, in the opinion of the principal investigator, makes the subject unsuitable for the study.

Subjects meeting any of the following additional criteria must not be enrolled in the **control or treatment holiday groups** in the study:

1. **SLE:** New mild-moderate or severe flare as defined by the SLE Flare Index during the 30 day screening period prior to Day 0.
2. **Steroids:** Prednisone (or prednisone equivalent) greater than 20mg/day within the 30 day screening period.
3. **New agents:** Any new immunosuppressive/immunomodulatory agent, anti-malarial, or NSAID within the 30 day screening period prior to Day 0. However, any NSAID use for < 1 week is allowed.

4.4. Withdrawal Criteria

A subject may voluntarily discontinue participation in this study at any time or may be withdrawn at the discretion of the investigator. Record the primary reason for withdrawal in the electronic case report form (eCRF).

Subjects in the treatment holiday and control groups will be withdrawn from the study for:

- Pregnancy: positive urine pregnancy test.
- Clinically significant, potentially life-threatening (Grade 4) AE that in the clinical judgement of the investigator is possibly, probably or definitely related to belimumab.
- Liver chemistry abnormalities. Refer to details regarding liver chemistry abnormalities and withdrawal as specified in Section [6.4.1](#).

- Laboratory parameters: Demonstrate clinically important changes in laboratory parameters.
- Prohibited concurrent medication or therapy.

These subjects will complete the Week 52 Exit visit (except for dosing with belimumab) at the time of discontinuation and the 16-week follow-up visit assessments at least 16 weeks after the withdrawal visit or last dose of belimumab as appropriate (see Section 6). The 6 month follow-up visit is scheduled only for those subjects in the treatment holiday or control groups.

Subjects in the long-term discontinuation group will be withdrawn from the study for:

- Pregnancy: positive urine pregnancy test.
- Laboratory parameters: Demonstrate clinically important changes in laboratory parameters.
- Have developed clinical evidence of significant, unstable or uncontrolled, acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases), or experienced an adverse event (AE) that could, in the opinion of the principal investigator, put the subject at undue risk.
- Have developed any other medical diseases (e.g., cardiopulmonary), laboratory abnormalities, or conditions (e.g., poor venous access) that, in the opinion of the principal investigator, makes the subject unsuitable for the study.

These subjects will complete the Week 52 visit assessments (see Section 6).

Subjects in the treatment holiday group are anticipated to be temporarily withdrawn from belimumab treatment for the initial 24 week holiday period of this study but therapy with belimumab 10 mg/kg can be reintroduced before the Week 24 visit if the subject's condition worsens or meets the definition of a severe flare as per the SLE flare index (Appendix 1). Subjects in the treatment holiday group who re-start belimumab treatment before the end of the 24-week holiday period will escape to the maintenance part of this study to receive further belimumab therapy.

The investigator must make every reasonable attempt to re-start belimumab therapy at the Week 24 visit. Any subject in the treatment holiday group who remains off-therapy with belimumab at the Week 24 visit can still be treated with belimumab from Week 28 onwards.

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

Belimumab for intravenous (IV) infusion will be supplied in glass vials by GSK. The contents of the label will be in accordance with all applicable regulatory requirements. Detailed instructions on the preparation, administration and storage of belimumab are provided in the Pharmacy Manual. Belimumab IV solution should be prepared by a pharmacist. Reconstitute the 400 mg single use vial of belimumab with 4.8 mL sterile water for injection to yield a final concentration of belimumab 80 mg/mL. Remove an amount of normal saline from the infusion bag equivalent to the amount of belimumab to be added, add the reconstituted belimumab, and gently invert the infusion bag to mix the solution. After reconstitution and dilution in normal saline, the material is stable for up to 8 hours at 2-8°C or at room temperature. The characteristics of belimumab are summarized in [Table 1](#).

Table 1 Belimumab Characteristics

Property	Belimumab
Formulation	Belimumab 400 mg per vial plus excipients (citric acid/sodium citrate/sucrose/polysorbate)
Dosage Form	Reconstituted solution
Unit dose strength	400 mg per vial (to contain 80 mg/mL when reconstituted with 4.8mL sterile water for injection [SWFI])
Physical description	White uniform lyophilised cake in a 20 mL vial
Manufacturer	Human Genome Sciences, Inc.
Route of administration	Intravenous

Subjects enrolled in the treatment holiday group will receive treatment with belimumab 10 mg/kg from Week 24 onwards **after** the initial 24-week treatment holiday period of the study has elapsed (see Section 3.1). At the start of the belimumab reintroduction period, subjects in the treatment holiday group will receive belimumab 10 mg/kg IV infused for over 1 hour every 28 days.

Subjects in the control group will receive belimumab 10 mg/kg IV infused for over 1 hour every 28 days from Day 0 onwards. Subjects in this group must be able to receive their first dose of belimumab on Day 0 of this study 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the BEL114333 open-label continuation study.

Subjects in the long-term discontinuation group will not receive belimumab at any point in this study.

The dose of belimumab administered may not be altered but the rate of infusion may be slowed or interrupted if the subject appears to develop signs of adverse reaction or infusion-associated symptoms. Do **not** increase the rate of infusion above the recommended rate.

Monitor the subject 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. Trained rescue personnel and rescue medications/equipment should be available for a minimum of the first dose.

Consider administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions for subjects who have previously received intravenous immunoglobulins (IVIG) or subjects with a history of allergies (allergic responses to food, drugs, insects, or a history of urticaria). The dose of belimumab may be delayed by up to 2 weeks or the dose may be withheld if the subject experiences a clinically significant AE that, in the clinical judgement of the investigator, is possibly, probably or definitely related to belimumab, and this AE continues at the next scheduled dose, or could potentially be exacerbated by the next dose. If a similar concern is present at the time of the next scheduled dose, the investigator and Medical Monitor will discuss whether to discontinue treatment with belimumab.

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request. Belimumab should be diluted to 250 mL normal saline after reconstitution, using a typical approved plastic intravenous administration set for the infusion.

Belimumab must be stored in a secure area under the appropriate physical conditions for the product, which includes storage in a refrigerator at a temperature of 2-8°C. Maintenance of a temperature log (manual or automated) is required. Access to and administration of belimumab will be limited to the investigator and authorized site staff. Belimumab must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Destroy all used belimumab vials according to site guidelines for the destruction of investigational products, after the monitor has conducted a check of the product accountability log during the study. At the end of the study, unused belimumab vials will be destroyed on site at the study closeout visit, after the monitor has conducted final belimumab accountability and given the site approval to destroy all remaining supplies.

5.2. Treatment Assignment

This is an open-label, non-randomized study. Site personnel will access the interactive voice response system (IVRS) to enrol the subject in the study and to log subject visits. Supplementary information is provided in the Study Procedures Manual (SPM).

5.3. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of

investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

5.4. Treatment Compliance

All doses administered within the study unit will be administered under the supervision of the investigator, designee or study nurses and the data entered into the electronic case report form (eCRF).

Drug dispensing /accountability logs will be maintained by the separate pharmacist or pharmacy designee.

5.5. Concomitant Medications and Non-Drug Therapies

Record all concomitant medications taken during the study in the eCRF.

5.5.1. Permitted Medications and Non-Drug Therapies

Subjects in the treatment holiday and control groups must be on a stable SLE treatment regimen during the 30 day screening period prior to Day 0.

After Day 0, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically required in response to improving or worsening conditions for the treatment holiday and control groups.

Note: Live vaccines are permitted for subjects in the long-term discontinuation group. Subjects in the control and treatment holiday groups are prohibited from receiving live vaccines.

5.5.2. Prohibited Medications and Non-Drug Therapies

Subjects in the **treatment holiday and control groups** who start prohibited medications or therapies at any time during the study must be withdrawn from the study. These subjects will return for the EXIT visit, and the follow-up visits 16 weeks and 6 months after receiving their last dose of belimumab as described in Section 4.4.

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-enrolment into another study of an investigational agent or non-drug therapy that may interfere with the conduct of this protocol.
- Anti-TNF or anti-IL-6 therapy (e.g., adalimumab, etanercept, infliximab, tocilizumab).
- Other biologics (e.g., rituximab, abatacept, interleukin-1 receptor antagonist [anakinra]).

- Intravenous immunoglobulin (IVIG).
- IV cyclophosphamide.
- Plasmapheresis, leukapheresis.

5.6. Treatment after the End of the Study

Eligible subjects in the treatment holiday and control groups may continue to receive belimumab therapy every 4 weeks under the maintenance phase of this protocol until the subject withdraws from the study, or the subject elects to participate in another belimumab continuation study for SLE, or the Sponsor discontinues the maintenance phase of the study for China subjects with the provision for China subjects to elect to participate in a different protocol to continue to receive belimumab, or belimumab becomes commercially available in a subject's country of participation, or upon the decision by the sponsor to discontinue the study. Safety reporting will be as specified in the protocol the subject participates in. Subjects in the treatment holiday and control groups who complete Week 52 of this study are not eligible to receive further treatment with belimumab in the maintenance phase of this study if belimumab is commercially available in the subject's country of participation.

No treatment with belimumab at end of this study is anticipated for subjects in the long-term discontinuation group since they did not receive belimumab therapy in this study.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition whether or not GSK is providing specific post study treatment.

5.7. Treatment of Study Treatment Overdose

The dose of belimumab considered to be an overdose has not been defined. There are no known antidotes and GSK does not recommend a specific treatment in the event of a suspected overdose. The investigators will use clinical judgement in treating the symptoms of a suspected overdose.

The approved product label for belimumab states for overdosage "There is no clinical experience with overdosage of BENLYSTA. Two doses of up to 20 mg/kg have been given by intravenous infusion to humans with no increase in incidence or severity of adverse reactions compared with doses of 1, 4, or 10 mg/kg".

6. STUDY ASSESSMENTS AND PROCEDURES

All subjects will attend clinic visits for efficacy and safety assessments every 4weeks for 52 weeks (see [Table 2](#)).

Subjects in the treatment holiday and control groups will be dosed with belimumab at the Week 52 visit in [Table 2](#) only if they are continuing belimumab therapy in the maintenance phase of this study. Subjects in the treatment holiday and control groups who wish to continue belimumab therapy after the Week 52 visit, will proceed to the Week 4 visit in [Table 3](#) (Time and Events Table for additional years) and continue to cycle through clinic visits from Week 4 through Week 48 in [Table 3](#) on an annual basis (see [Section 3.1](#)). Subjects in the treatment holiday and control groups who do not wish to continue belimumab therapy after Week 48 will proceed to the Week 52 (Exit) visit but will not be dosed with belimumab.

Subjects in the treatment holiday and control groups who meet the protocol-defined withdrawal criteria specified in [Section 4.4](#) at any time during Year 1 or the additional years will undergo assessments scheduled at the Exit visit (Week 52) in [Table 2](#) **except** for dosing with belimumab. At approximately 16 weeks after the withdrawal visit or the last dose of belimumab as appropriate, these subjects will also undergo the assessments scheduled at the 16-week follow-up visit; the 6 month follow-up visit is scheduled only for these discontinued subjects in the treatment holiday or control groups.

Subjects in the long-term discontinuation group will attend for clinic visits from Day 0 through Week 52 in [Table 2](#) only. The 16-week and 6-month follow-up visits do not apply to this group. Subjects in the long-term discontinuation group who meet the protocol-defined withdrawal criteria specified in [Section 4.4](#) at any time during Year 1 will undergo assessments scheduled at the Exit visit (Week 52) in [Table 2](#).

Table 2 Time and Events Table (Year 1)

	Screen	Treatment Holiday Study														Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	--	--
Study Day	Up to -30 ¹	0 ²	28 ±7d	56 ±7d	84 ±7d	112 ±7d	140± 7d	168 ±7d	196± 7d	224 ±7d	252 ±7d	280± 7d	308 ±7d	336 ±7d	364 ±7d or Exit	16-wk ±7d ³	6 mo ±7d
Study Week		0	4	8	12	16	20	24	28	32	36	40	44	48	52	--	--
Written Informed Consent ⁴	X																
Demography		X															
Medical History		X															
SLE History		X															
Therapy History		X															
Physical Examination		X															
Inclusion/Exclusion		X															
Efficacy Assessments																	
DAS: SS, SLE Flare Index, PGA ⁵	X ¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
SLICC/ACR Damage Index		X						X							X		
Safety Assessments																	
Vital Signs ⁶		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, height ^{6,7}		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	
Record Concurrent Medications		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	
Laboratory Assessments																	
Haematology & Modified Chem 20 (non-fasting) ⁶	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spot urine (protein to creatinine ratio) ⁸	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test ^{6,9}	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	
Pharmacogenetic Sampling ¹⁰		X															
aCL Autoantibody		X													X		
C3/C4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	Screen	Treatment Holiday Study														Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	--	--
Study Day	Up to -30 ¹	0 ²	28 ±7d	56 ±7d	84 ±7d	112 ±7d	140± 7d	168 ±7d	196± 7d	224 ±7d	252 ±7d	280± 7d	308 ±7d	336 ±7d	364 ±7d or Exit	16-wk ±7d ³	6 mo ±7d
Study Week		0	4	8	12	16	20	24	28	32	36	40	44	48	52	--	--
Anti-dsDNA Autoantibodies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ANA Autoantibodies		X						X							X		
IgG, IgA & IgM ¹¹		X		X		X		X		X		X		X	X		
PT/ PTT		X															
Exploratory Lab Assessments																	
Pharmacokinetic Sampling ¹²		X		X		X		X ¹²		X					X ¹²		
Immunogenicity ^{6, 13}		X			X		X ¹³	X		X					X	X	X ¹³
BlyS Protein ¹⁴						X		X		X							
B cell Markers ¹⁵		X		X		X		X		X		X			X		X
Investigational Product (IP)																	
IP Administration ¹⁶		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

DAS = disease activity scales; SS = SELENA SLEDAI; SLE = systemic Lupus Erythematosus; PGA = Physician's Global Assessment; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology; ALT = alanine aminotransaminase; AST = aspartate aminotransaminase; PT/PTT = prothrombin time/partial thromboplastin time; BlyS = B Lymphocyte Stimulator; IP = investigational product; aCL = anticardiolipin

1. A screening visit of up to 30 days prior to the Day 0 visit will be scheduled for subjects in the treatment holiday and control groups for assessment of SELENA SLEDAI score to assess eligibility.
2. The EXIT Visit in the respective feeder continuation studies will serve as the Day 0 visit for all 3 subject groups in this study. Assessments covered for both this study at Day 0 and the Exit visit of the feeder continuation studies need only be performed once and recorded in the appropriate case report forms for each study. Subjects in the control group must be able to receive the 1st dose of belimumab on Day 0 of this study on average 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the feeder continuation study.
3. The 16 week follow-up visit will occur at approximately 16 weeks after last dose of investigational product for subjects in the control group who withdraw at any time during the study, or for subjects in the treatment holiday group who withdraw from the study from Week 24 onwards (Visit 7) during the belimumab re-introduction period. The 16-week and 6 month follow-up visits do not apply to subjects in the long-term discontinuation group.
4. Obtain written informed consent to participate in this study at the Screening visit.
5. Guidelines for scoring proteinuria for SELENA SLEDAI are provided in Section 6.3.1.1.
6. Complete assessment prior to belimumab dosing for subjects in the control group (to Week 48) and for subjects in the treatment holiday group (during Weeks 24 to 48 or earlier in the event of a flare). Immunogenicity testing includes quantifying the amount of belimumab present in the samples using the belimumab PK assay.
7. For any subject whose weight changes by more than 5% from that recorded at Day 0, use the weight at the current visit for calculating the belimumab dose to be administered. Height measured only at Day 0.

8. A 24-hour urine may be done as an additional assessment if clinically indicated (e.g., renal flare).
9. Urine pregnancy test results for women of child-bearing potential must be available prior to dosing (during Weeks 0 to 48 in the control group and during Weeks 24 to 48 or earlier in the event of a flare in the treatment holiday group). Can be performed at any time during the visit for females of child-bearing potential in the long-term discontinuation group.
10. PGx sampling from consenting subjects recruited from all studies except from study BEL114333. PGx informed consent must be obtained prior to sampling.
11. Serum immunoglobulin isotypes: IgG, IgM, IgA.
12. Pharmacokinetic sampling at select sites for subjects in the control and treatment holiday groups; subjects in the treatment holiday group can have PK sampling performed at any time during the visit between Weeks 0 and 16. Otherwise, if on a dosing day, sampling must be performed **prior** to dosing. Collect blood samples pre-dose and post-dose at the end of the infusion at Weeks 24 and 52 (or earlier if belimumab is re-started before Week 24 in the event of a severe flare by using the escape option). Subjects in the long-term discontinuation group will have one PK sampling performed at any time during the visit between Weeks 0 and 24. PK sampling for the long-term discontinuation group is not performed after Week 24. Long-term discontinuation subjects withdrawing before Week 24 will have one PK sampling performed at any time during the EXIT visit. PK sampling for long-term discontinuation subjects withdrawing after Week 24 is not performed at the EXIT visit.
13. Blood sample for immunogenicity will be taken at Weeks 12, 24, 36 and 52 for all three groups. In addition, a blood sample for immunogenicity will also be taken **4 weeks prior** to the reintroduction of belimumab (at Week 20 since belimumab will be reintroduced at Week 24) in the treatment holiday group. A blood sample for immunogenicity must be taken at least 6 months after the final dose of investigational product for any subjects in the control group or treatment holiday group who had an anti-belimumab antibody response at the 16-week follow-up visit (or at the last immunogenicity assessment if 16-week follow-up is not available). **Note** that serum samples for immunogenicity must be collected pre-dose at the time of dosing from subjects in the treatment holiday group who experience a severe flare prior to Week 24 and consequently receive open-label belimumab as rescue. Immunogenicity blood sample will not be collected at the 6-month follow up visit for subjects in the long-term discontinuation group as this visit does not apply to this subject group.
14. Measured in treatment holiday group at Weeks 16 and pre-dose at Week 24. Measured in long-term discontinuation group at Weeks 16, 24 and 32. Not measured in control group.
15. Biological Markers include 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 and CD20-/138+ plasma cells). Note: B cell markers will not be collected at the 6-month follow up visit for subjects in the long-term discontinuation group as this visit does not apply to this subject group.
16. Only subjects in the control group will receive belimumab 10 mg/kg during Weeks 0 through 20 inclusive; subjects in the control group must be able to receive the **first** dose of belimumab **in this study** 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in their **previous** open-label continuation study. Subjects in the control group and treatment holiday groups will receive belimumab from Weeks 24 through 48 although subjects in the treatment holiday group may be treated with belimumab **prior** to Week 24 as determined by the investigator in the event of increased SLE activity. When belimumab therapy is re-started, subjects in the treatment holiday group will remain under clinical supervision for 3 hours after completion of the first 2 infusions. At the **Week 52** visit, only subjects in the treatment holiday and control groups who are continuing belimumab therapy beyond this time will be dosed.

Table 3 Time and Events Table (Additional Years)

Study Visit (Weeks) ¹	4	8	12	16	20	24	28	32	36	40	44	48
Study Day	28 ±7d	56 ±7d	84 ±7d	112 ±7d	140 ±7d	168 ±7d	196 ±7d	224 ±7d	252 ±7d	280 ±7d	308 ±7d	336 ±7d
Efficacy Assessments												
Disease Activity Scales: SELENA SLEDAI, SLE Flare Index, and PGA ²						X						X
SLICC/ACR Damage Index												X
Safety Assessments												
Symptom-driven Physical Exam						X						X
Record Concurrent Medications	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
Vital Signs ^{3,4}	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments												
Haematology & Modified Chem 20 (non-fasting) ^{3,5}						X						X
Urinalysis ^{5,6}						X						X
Spot urine (protein to creatinine ratio) ^{3,5,6}						X						X
Urine Pregnancy Test ^{3,5,7}	X	X	X	X	X	X	X	X	X	X	X	X
C3, C4, Anti-dsDNA Autoantibodies ^{3,5}						X						X
IgG ^{3,5,8}												X
IgA & IgM ^{3,5,8}												X
Exploratory Lab Assessments												
Immunogenicity ^{3,9}						X						X
B cell Markers ¹⁰												X
Investigational Product												
Belimumab Administration ^{4,11}	X	X	X	X	X	X	X	X	X	X	X	X

1. Calendar represents a yearly (48-week) ongoing visit schedule until the subject is terminated from the study.
2. Guidelines for scoring proteinuria for SELENA SLEDAI are provided in Section 6.3.1.1.
3. Assessments performed prior to dosing.
4. For any subject whose weight changes by more than 5% from that recorded at Day 0, use the weight at the current visit for calculating the belimumab dose to be administered.
5. During "Additional years", investigators can obtain any of the same laboratory assessments that are mentioned for Year 1 (haematology, modified Chem 20, urinalysis, spot urine to creatinine ratio, urine pregnancy, C3, C4, anti-ds DNA autoantibodies, IgG, IgA, and IgM), as unscheduled laboratory tests at any time during Year 2 and beyond, if clinically indicated. Any additional laboratory tests beyond this, if not related to the protocol, will be the responsibility of the investigator and subject.
6. A 24-hour urine may be done as an additional assessment if clinically indicated (e.g., renal flare).
7. Results of urine pregnancy tests in women of child-bearing potential must be available prior to belimumab dosing.
8. Serum immunoglobulin isotypes: IgG, IgM, IgA.
9. Immunogenicity testing includes quantifying the amount of belimumab present in the samples using the belimumab PK assay.
10. Biological Markers include FACS of peripheral lymphocytes: B lymphocytes (CD20+, CD20+/27+ memory, CD20+/27- naïve, CD20+/69+ activated, CD20+/138+ plasmacytoid, CD19+/27BRIGHT/38BRIGHT SLE subset and CD20-/138+ plasma cells).
11. After completion of the Week 48 visit during year 1 of the study, subjects in the treatment holiday and control groups can continue to receive belimumab therapy at 4-weekly intervals in the maintenance phase of this study. Subjects who withdraw from belimumab therapy during this maintenance phase will complete the Exit and follow-up visits detailed in the Year 1 Time and Events Table (Table 2). The Exit visit Schedule should be scheduled 4 weeks after the final belimumab dose and the 16-week follow-up visit 16 weeks after the final belimumab dose.

6.1. Endpoints

6.1.1. Primary Endpoints

The primary efficacy endpoint is time to any SLE Flare Index flare.

6.1.2. Secondary Endpoints

The secondary endpoints are:

- Rate of any SLE Flare Index flares.
- Time to first severe SLE Flare Index flare.
- Number of subjects in the treatment holiday and long-term discontinuation group with evidence of rebound (defined as a SELENA SLEDAI score during the first 24 weeks that exceeds the baseline SELENA SLEDAI score in the original parent study).
- Number of subjects with confirmed true positive belimumab anti-drug antibodies (ADA) by the end of the study.
- Percentage change from baseline in:
 - Total serum immunoglobulin (IgG, and other isotypes: IgM and IgA)
 - Autoantibodies (anti-dsDNA, ANA), and complement (C3, C4)
- Percent change in absolute B cell subsets (CD20+, CD20+/27+ memory, CD20+/27- naïve, CD20+/69+ activated, CD20+/138+ plasmacytoid, CD19+/27BRIGHT/38BRIGHT SLE subset and CD20-/138+ plasma cells) at Weeks 0, 8, 16, 24, 32, 40 and 52 and from Weeks 24 to 52.
- Absolute change in SELENA SLEDAI score.
- Number of days of daily prednisone dose ≥ 7.5 mg/day and/or increased by 25% from Day 0 of this study to Week 24, from Day 0 of this study to Week 52, and from Week 24 to Week 52.
- Number of days of daily prednisone dose ≤ 7.5 mg/day and/or decreased by 25% from Day 0 of this study to Week 24, from Day 0 of this study to Week 52, and from Week 24 to Week 52.

Note: baseline is the time before any treatment with belimumab, which was Day 0 of the original parent studies that fed into the 3 continuation studies from which subjects were recruited into this study. When Day 0 is used in relation to endpoints, this refers to Day 0 of this study.

6.1.3. Other Endpoints

- Change in SLICC/ACR Damage Index.
- Percentage change in PGA.
- Percentage change from baseline of prednisone dose at each scheduled visit.

- Percentage of subjects whose average prednisone dose was reduced to ≤ 7.5 mg/day from >7.5 mg/day at baseline.

6.1.4. Definitions of SLE Flares Used in This Study

SLE flares are defined as:

- SFI Flare: A mild/moderate or severe flare according to the modified SELENA SLEDAI SLE Flare Index (modified excludes severe flares from the SELENA SLEDAI flare assessment that were triggered only by an increase in SELENA SLEDAI score to >12).

A SLE renal flare is defined as the occurrence of 1 or more of the following in 2 or more consecutive visits during the study:

1. A reproducible increase in 24-hour urine protein equivalent levels to
 - >1 g if the Day 0 value was <0.2 g,
 - >2 g if the Day 0 value was 0.2 to 1 g, or
 - More than twice the value at Day 0 if the Day 0 value is >1 g.
2. A reproducible increase in GFR of $>20\%$ accompanied by at least one of the following: proteinuria (>1 g/24 hour equivalent), and/or cellular (RBC or WBC) casts [Alarcón-Segovia, 2003].

6.2. Critical Baseline Assessments

The screening phase of up to 30 days will allow an assessment of the SELENA SLEDAI score as part of the eligibility criteria for subjects in the treatment holiday and control groups.

The EXIT visit of the relevant SLE continuation protocol (BEL114333, HGS1006-C1066, or LBSL99) from which the subject is recruited will serve as the Day 0 visit in this study. Subjects in the control group will be dosed with belimumab at the Day 0 visit as part of this protocol. These subjects must be able to receive the Day 0 dose in this study 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the previous open-label continuation study. Any procedures from this protocol or from the relevant previous open-label continuation protocols to be performed pre-dose must be completed before dosing subjects in the control group. Obtain written informed consent from all subjects to participate in this study at the Screening visit.

Procedures necessary for the Day 0 visit of this protocol and for the last visit of the relevant SLE open-label continuation protocol from which the subject is recruited need only be performed once. Results from Day 0 procedures that are duplicated in the relevant SLE continuation study will be recorded in the eCRF for that study and must also be **transcribed** to the relevant eCRFs in this study. Additional Day 0 procedures exclusive to this study will be recorded directly in the eCRFs for this study.

6.3. Efficacy

Efficacy will be assessed from SELENA SLEDAI score, SLE flare index, Physician's Global Assessment (PGA) and SLICC/ACR damage index.

All site staff scoring SELENA SLEDAI assessments are required to pass proficiency tests before carrying out assessments to ensure consistency across centres.

6.3.1. SELENA SLEDAI

6.3.1.1. SELENA SLEDAI Score

The SELENA SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) used in this study is a slightly modified version of the SLEDAI developed for a National Institutes of Health sponsored multicentre study of estrogen/progesterone hormone use in women with SLE [[Buyon](#), 2005; [Petri](#), 2005]. The descriptions for some of the items are slightly modified, but the organ systems and weighted scores are the same as the published SLEDAI.

The SLEDAI is a validated index for assessing SLE disease activity [[Bombardier](#), 1992]. It is a weighted index in which signs and symptoms, laboratory tests, and physician's assessment for each of 9 organ systems are given a weighted score and summed, if present at the time of the visit or in the preceding 10 days:

- Score of 8 each for CNS and vascular items.
- Score of 4 each for renal and musculoskeletal items.
- Score of 2 each for serosal, dermal, and immunologic items.
- Score of 1 each for constitutional and hematologic items.

The maximum theoretical score for the SELENA SLEDAI is 105 (all 24 descriptors present simultaneously) with 0 indicating inactive disease. A copy of the index is provided in [Appendix 1](#).

Completion of the index requires collection of a 24-hour urine sample for assessment of proteinuria (although spot urine protein:creatinine ratio is commonly substituted in practice), measurement of anti-dsDNA, C3, C4, haematology, and urinalysis, and for subjects with myositis, CPK.

However, spot urine protein:creatinine ratio will be used for determining proteinuria for the SELENA SLEDAI in this study since there is a strong correlation between the protein content of a 24-hour urine collection and the protein:creatinine ratio in a single urine sample [[Ginsberg](#), 1983; [Ruggenti](#), 1998; [Clinical Practice Guidelines for Chronic Kidney Disease](#), 2002; [Price](#), 2005].

Scoring for proteinuria in the SELENA SLEDAI disease activity index will be in accordance with the following guidelines.

Scoring for Proteinuria at Screening for Eligibility

The proteinuria score for SELENA SLEDAI must be 0 at the most recent assessment performed in BEL114333. If at the screening visit the assessment of 24-hour proteinuria (by spot urine protein to creatinine ratio) shows >0.5 g/24 hour equivalent increase above the previous value (in BEL114333) or the subject develops new onset of proteinuria >0.5 g/24 hour equivalent, 4 points will be assigned at the screening assessment.

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 (i.e., baseline), the subject, by default, will have an improving SELENA SLEDAI score. 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:

- **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 urine protein to 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.

- **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 (i.e., 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.

6.3.1.2. Laboratory tests for SELENA SLEDAI

A strong correlation has been demonstrated between the protein content of a 24-hour urine collection and the protein:creatinine ratio in a single urine sample [Ginsberg, 1983; Ruggenenti, 1998; [Clinical Practice Guidelines for Chronic Kidney Disease](#), 2002; Price, 2005]. For this reason, spot urine protein:creatinine ratio will be used for determining proteinuria in this study for the SELENA SLEDAI 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 [[Clinical Practice Guidelines for Chronic Kidney Disease](#), 2002]. Therefore, GFR estimated by the Cockcroft-Gault formula will be used as was done in the Phase II trial of belimumab (LBSL02) and Phase III.

Cockcroft-Gault Equation [[Cockcroft](#), 1976]

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

Values outside the reference laboratory normal range that require the investigator's assessment of relationship to SLE:

6.3.1.3. SLE Flare Index

The SLE Flare Index categorizes SLE flare as “mild or moderate” or “severe” based on a positive assessment for at least one of 5 variables [[Buyon](#), 2005; [Petri](#), 2001; [Petri](#), 2005].

- Change in SELENA SLEDAI score from the most recent assessment to current (not used for severe flare).
- Change in signs or symptoms of disease activity.
- Change in prednisone dosage.
- Use of new medications for disease activity or hospitalization.
- Change in PGA score.

Hospitalization for SLE activity is an additional category included only for a severe flare.

A copy of the SLE Flare Index is provided in [Appendix 1](#).

6.3.1.4. Physician's Global Assessment (PGA)

The PGA is part of the validated SELENA SLEDAI index and is designed for the physician to indicate the subject's overall disease activity at a particular visit [[Petri](#), 1999]. The PGA is a 0-10 cm visual analogue scale (VAS), anchored at 0 (none) and 3 (severe), with intermediate lines at 1 (mild), and 2 (moderate). Each PGA measurement will be transformed linearly ($\times 3/10$) to obtain a value between 0.00 and 3.00.

The same primary investigator or same subinvestigator will evaluate and score the PGA for the subject each time, unless agreed otherwise with the GSK medical monitor.

A copy of the PGA VAS is provided in [Appendix 1](#).

6.3.2. SLICC/ACR Damage Index

The Systemic Lupus International Collaborative Clinics/American College of Rheumatology (SLICC/ACR) Damage Index is a validated instrument developed to assess the accumulated damage in patients with SLE, resulting from either the disease process or its sequelae. It can identify changes in damage seen in patients with both active and inactive disease and records damage occurring in patients with SLE regardless of its cause [[Gladman, 1996](#)]. The index is a predictor of severe outcome and an indicator of morbidity in different ethnic groups [[Stoll, 1996](#)]. SLICC/ACR Damage Index was designed to be useful both as a descriptor for patient populations included in studies, and as an outcome measure for therapeutic trials and studies of prognosis [[Gladman, 1996](#)].

The SLICC/ACR Damage Index consists of 39 items in 12 different organ systems. For a feature to represent damage, it must be present for at least 6 months, to enable discrimination between active inflammation and tissue damage [[Gladman, 1996](#)]

Scoring is usually 0 or 1, although in 6 items, a score of 2 can be given if there is a repeat episode more than 6 months apart. The exception is end-stage renal disease, which scores 3.

A copy of the SLICC/ACR Damage Index is provided in [Appendix 2](#).

6.4. Safety

The safety assessments are adverse events (AEs) (including infusion-related and hypersensitivity reactions, infections and malignancies), haematological and clinical chemistry parameters, urinalysis, B cell markers, immunogenicity, vital signs (including weight), and physical examinations.

6.4.1. Liver chemistry stopping and follow up criteria

Phase III-IV liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance) [[James, 2009](#); [Le Gal, 2005](#)]. For subjects in the treatment holiday group having belimumab therapy re-introduced from Week 24 onwards or escaping to the maintenance phase of the study prior to Week 24, subjects in the control group, or any subject entering the maintenance phase of the study, the following applies:

Phase III-IV liver chemistry stopping criteria 1-5 are defined below and in [Appendix 3](#):

1. ALT \geq 3xULN **and** bilirubin \geq 2xULN (>35% direct bilirubin) (or ALT \geq 3xULN **and** INR>1.5, if INR measured)

NOTE: if serum bilirubin fractionation is not immediately available, withdraw belimumab for that subject if ALT \geq 3xULN and bilirubin \geq 2xULN. Serum bilirubin fractionation should be 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.

2. ALT \geq 8xULN.

3. ALT \geq 5xULN but <8 xULN persists for \geq 2 weeks OR ALT \geq 3xULN but <5 xULN persists for \geq 4 weeks

4. ALT \geq 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

5. ALT \geq 5xULN but <8 xULN and cannot be monitored weekly for \geq 2 weeks OR ALT \geq 3xULN but <5 xULN and cannot be monitored weekly for \geq 4 weeks

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately** discontinue belimumab for that subject
- Report the event to GSK **within 24 hours**
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT \geq 3xULN **and** bilirubin \geq 2xULN (>35% direct) (or ALT \geq 3xULN **and** INR>1.5, if INR measured); INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).**

NOTE: if serum bilirubin fractionation is not immediately available, withdraw belimumab for that subject if ALT \geq 3xULN **and** bilirubin \geq 2xULN. Serum bilirubin fractionation should be 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.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Do not restart subject with belimumab unless GSK Medical Governance approval is granted (refer to Section 6.4.1.1)

Monitoring for liver chemistry stopping criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring

- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values

Monitoring for liver chemistry stopping criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Phase III-IV Liver Chemistry Increased Monitoring Criteria With Continued Therapy

Subjects with ALT $\geq 5xULN$ 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 $\geq 3xULN$, but $< 5xULN$ 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
- Can continue belimumab
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If ALT decreases from ALT $\geq 5xULN$ and $< 8xULN$ to $\geq 3xULN$ 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 values.

Follow-up Assessments For Liver Stopping Criteria 1-5

Make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
 - 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
- 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. **NOTE:** 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](#)].
- Blood sample for PK analysis, obtained within approximately one to two weeks after the liver event. Record the date/time of the PK blood sample draw and the date/time of the last dose of belimumab prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin $\geq 2xULN$.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

The following are required for subjects with ALT $\geq 3xULN$ and bilirubin $\geq 2xULN$ (>35% direct) or ALT $\geq 3xULN$ **and** INR>1.5, if INR measured; but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and 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 computerized tomography) to evaluate liver disease.

For long-term discontinuation group subjects found to have met the liver stopping criteria without receiving belimumab, investigators will apply the withdrawal criteria in Section [4.4](#).

6.4.1.1. Study Treatment Restart

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 is signed by the subject

If GSK Medical Governance approval to restart 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 drug induced liver injury [DILI]) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, 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 6.4.7.

6.4.2. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. Subjects will also be issued a paper diary to record adverse events and concomitant medications during the study. This will be used to assist subject recall in discussions with the investigator, for site staff to then enter as appropriate in the eCRF.

6.4.2.1. Definition of an AE

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

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

“Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

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

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

6.4.2.2. Definition of a SAE

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

- a. Results in death
- b. Is life-threatening

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

- c. Requires hospitalization or prolongation of existing hospitalization

NOTE: 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

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

- e. Is a congenital anomaly/birth defect
- f. Medical or scientific judgement 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 \geq 3xULN **and** bilirubin \geq 2xULN (>35% direct) (or ALT \geq 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 \geq 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.

6.4.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

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

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs, including but not limited to:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thrombosis
- Deep Venous Thrombosis
- Revascularization
- Hypersensitivity reactions

- Herpes zoster
- Malignancies

This information should be recorded within one week of when the AE/SAE(s) are first reported.

6.4.4. Death Events

In addition, all deaths, whether or not they are considered SAEs, will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

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

The following conditions (preferred terms; MedDRA v. 14.0) are disease-related events (DRE) 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 6.4.10. However, because these events are typically associated with the disease under study, 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).

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

6.4.6. Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

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

Female subjects who become pregnant during the study, should not be treated with belimumab and must be withdrawn from the study (see Section 4.4). Female subjects in the long-term discontinuation group who become pregnant during the study must still be withdrawn from the study despite not being treated with belimumab during the initial 52 weeks of the study (see Section 4.4).

6.4.7. Time Period and Frequency of Detecting AEs and SAEs

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

AEs will be collected from the start of the study (Day 0) and until the 16-week follow up contact for subjects in the treatment holiday and control groups or until the Week 52 visit for subjects in the long-term discontinuation group.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.4.10. **Note:** for China sites, serious AEs should be recorded from the time the consent form is signed until the 16-week follow up contact for subjects in the treatment holiday and control groups, or until the Week 52 visit for subjects in the long-term discontinuation group. GSK's pharmacovigilance safety database will contain all SAEs occurring after the first dose of investigational product plus any SAEs related to study participation occurring after the subject signs the informed consent form. SAEs that occur after signing the informed consent form but before the first dose of investigational product that are not considered to be related to study participation will not be entered into the GSK pharmacovigilance safety database, and will be summarized separately in the clinical study report.

6.4.8. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

“How are you feeling?” or for paediatric studies, “How does your child seem to feel?”

“Have you had any (other) medical problems since your last visit/contact?” or for paediatric studies, “Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?” or for paediatric studies, “Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?”

6.4.9. Investigator Evaluation of Adverse Events

The investigator will evaluate all adverse events with respect to seriousness (criteria for serious are listed in Section 6.4.2.2), severity (intensity) and causality (relationship to belimumab). The investigator will make an assessment of intensity for each AE and SAE based on the Division of Microbiology and Infectious Diseases (DMID) Adverse Event Severity Grade Tables (see [Appendix 4](#)), 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 discomfoting to interfere with normal everyday activities (Grade 2 DMID)

Severe - An event that prevents normal everyday activities (Grade 3 or 4 DMID)

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.

6.4.10. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	“SAE” data collection tool “CV events” and/or “death” data collection tool(s) if applicable	24 hours	Updated “SAE” data collection tool “CV events” and/or “death” data collection tool(s) if applicable
Pregnancy	2 weeks	“Pregnancy Notification Form”	2 weeks	“Pregnancy Follow-up Form”
Non-serious adverse events related to study treatment	5 calendar days	“Adverse Reaction” data collection tool	2 weeks	Updated “Adverse Reaction” data collection tool
DRE	2 weeks ⁴	DRE CRF	2 weeks ⁴	Updated DRE CRF
<i>Liver chemistry abnormalities for Phase I to IV:</i>				
ALT \geq 3xULN and Bilirubin \geq 2xULN (>35% direct) (or ALT \geq 3xULN and INR>1.5, if INR measured) ¹	24 hours ²	“SAE” data collection tool. “Liver Event CRF” and “Liver Imaging” and/or “Liver Biopsy” CRFs, if applicable ³	24 hours	Updated “SAE” data collection tool/“Liver Event” Documents ³
<i>Remaining liver chemistry abnormalities Phase III to IV:</i>				
ALT \geq 8xULN; ALT \geq 3xULN with hepatitis or rash or \geq 3xULN and <5xULN that persists \geq 4 weeks	24 hours ²	“Liver Event” Documents (defined above) ³	24 hours	Updated “Liver Event” Documents ³
ALT \geq 5xULN plus bilirubin <2xULN	24 hours ²	“Liver Event” Documents (defined above) do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks ³	24 hours	Updated “Liver Event” Documents, if applicable ³
ALT \geq 5xULN and bilirubin <2xULN that persists \geq 2 weeks	24 hours ²	“Liver Event” Documents (defined above) ³	24 hours	Updated “Liver Event” Documents ³

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
ALT \geq 3xULN and <5x ULN and bilirubin <2xULN	24 hours ²	“Liver Event” Documents (defined above) do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks ³	24 hours	Updated “Liver Event” Documents, if applicable ³

1. INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.
2. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety
3. Liver Event Documents (i.e., “Liver Event CRF” and “Liver Imaging CRF” and/or “Liver Biopsy CRF”, as applicable) should be completed as soon as possible.
4. The SRT (or Study Team, if there is no SRT) should determine the appropriate time frame, *if one is needed*, for completion of DRE CRF pages.

Liver chemistry stopping and follow-up criteria are provided in Section 6.4.1.

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

6.4.10.1. Regulatory reporting requirements for SAEs

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

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK 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 GSK policy and are forwarded to investigators as necessary.

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

6.4.11. Laboratory Evaluations

Collect samples (blood and urine) for clinical laboratory tests as specified in the appropriate Time and Events schedule ([Table 2](#) or [Table 3](#)). Additional samples may be taken for safety reasons at the discretion of the Investigator. Clinical laboratory tests will consist of a complete blood count (CBC) with differential, Chem-20, magnesium, and urinalysis as listed in [Appendix 5](#).

All protocol required laboratory assessments, as defined in [Appendix 5](#), must be performed by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the subject's eCRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

6.4.12. Infusion-related Reactions and Hypersensitivity Reactions

Infusion-related reactions on the day of an infusion occurred in approximately 17% of patients treated with belimumab 1mg/kg or 10mg/kg during the double-blind portion of the Phase 2 and 3 SLE studies, but at rates similar to placebo (15%). Most infusion-related/hypersensitivity events have been mild-moderate in nature; however, severe and or serious events have been reported infrequently (<2% of patients). These events have included reports of rash, urticaria, angioedema, hypotension and anaphylaxis. As has been done in recent protocols, this protocol recommends that administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions should be considered for subjects with a history of allergies or urticaria.

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects in the treatment holiday group should remain under clinical supervision for 3 hours after completion of the first 2 infusions when re-starting belimumab, whether upon receiving as 'rescue' after a severe flare or upon returning for the Week 24 visit and re-introduction of belimumab. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. Subjects should be made aware of the potential risk, including the risk of delayed reactions, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

In addition, delayed-type, non-acute hypersensitivity reaction have also been observed and included symptom s such as rash, nausea, fatigue, myalgia, headache, and facial oedema.

6.4.13. Other Immunosuppression Related Considerations

Although there is no evidence to date for an increased risk with belimumab treatment, the possibility of immunosuppression resulting in an increase in the frequency and/or severity of infection and/or an increased risk of malignancy cannot be excluded. During the trial, subjects will be questioned at all study visits about adverse events and results recorded in the eCRF. Examinations and laboratory evaluations will be performed routinely and the results, including markers of potential immunosuppression, will be reported to the investigators.

6.4.13.1. 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.

6.4.14. Vital Signs and Weight

Measure systolic and diastolic blood pressure (sitting), heart rate, temperature and weight. Oral or tympanic temperatures are acceptable, but the method for each subject should remain consistent. Axillary temperatures are not permitted. Vital sign and weight measurements must be taken pre-dose at all dosing visits. For non-dosing visits, vitals and weight assessment can be performed at any time during the subject's visit. For any subject whose weight changes by more than 5% from that recorded at the Day 0 visit, the weight at the current visit will be used to calculate the belimumab dose to be administered at this dosing visit. At the discretion of the investigator, vital signs may be assessed at unscheduled visits.

6.4.15. Physical examination

As a minimum, brief physical examination will include assessment of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). At the discretion of the investigator, physical examinations may be assessed at unscheduled visits.

6.4.16. Immunogenicity

Serum samples will be collected for immunogenicity assessment. All samples should be collected prior to dosing (where appropriate) as specified in the appropriate Time and Events schedule ([Table 2](#) or [Table 3](#)). Note that serum samples for immunogenicity must be collected pre-dose at the time of dosing from subjects in the treatment holiday group who experience a severe flare prior to Week 24 and consequently receive open-label

belimumab as rescue. For non-dosing visits, assessment can be performed at any time during the visit. An attempt will be made to determine the amount of belimumab (PK) present in immunogenicity samples with confirmed anti-drug binding antibodies (ADA). The belimumab level in these samples will be used in the interpretation of ADA results and will be included in the immunogenicity section in the CSR.

An attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of belimumab for any subject who had an anti-belimumab antibody response at the 16-week follow-up visit or if the 16-week follow-up immunogenicity sample is not available.

All immunogenicity testing will be carried out according to the multi-tier assay testing scheme including the detection of anti-drug binding antibodies (ADA, including 3-steps of screening, confirmation/specificity and titration) and the detection of anti-drug neutralizing antibodies (Nab). **Note:** Nab testing will not be performed in China.

All samples will be tested in ADA screening step. Any samples tested positive in the screening step will then be tested using an ADA confirmation step. Any confirmed positive samples in the confirmation will be further tested in the titration to obtain ADA titer values and in the Nab assay to evaluate the presence of neutralizing antibodies. The incidence of subjects with confirmed positive ADA responses with titers and positive Nab will be reported, respectively at the end of the study. However, Nab results will not be available for China subjects.

Details for sample processing and analysis are provided in the SPM.

6.5. Biomarkers

As yet, no clear surrogate endpoints have been widely accepted that clearly define clinical outcomes for the multi-organ system manifestations of SLE. However autoantibodies have been shown to be important early markers of specific disease processes or severity in SLE [Hahn, 1998; Leslie, 2001; Ravirajan, 2001] and are associated with disease activity [Villarreal, 1997]. Therefore autoantibody levels will be included as endpoints.

Collect blood samples as specified in the appropriate Time and Events schedule (Table 2 or Table 3), in order to assess the following endpoints:

- Percent change from baseline:
 - Total serum immunoglobulin (IgG and other isotypes: IgM and IgA).
 - Autoantibodies (anti-dsDNA) and complement (C3, C4).
- Percent change 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 and CD20-/138+ plasma cells).

All biomarker samples will be analysed centrally.

6.6. Pharmacokinetics

Collect blood samples for measurement of serum belimumab concentrations from subjects in the treatment holiday and control groups at selected sites at the times specified in the Time and Events Table (Table 2). Only one PK sampling for the treatment holiday group between Weeks 0 and 16 can be performed at any time during the visit. Otherwise, sampling must be performed prior to dosing (pre-dose sample) at Day 0 and Weeks 8 and 16. Sampling must be performed pre-dose and post-dose (at the end of the belimumab infusion) at Weeks 24 and 52 (or earlier if belimumab is re-started before Week 24 in the event of a severe flare by using the escape option). For non-dosing visits, assessment can be performed once at any time during the subject's visit. Subjects in the long-term discontinuation group will have one PK sampling performed at any time during the visit between Weeks 0 and 24. PK sampling for the long-term discontinuation group is not performed after Week 24. Long-term discontinuation subjects withdrawing before Week 24 will have one PK sampling performed at any time during the EXIT visit. PK sampling for long-term discontinuation subjects withdrawing after Week 24 is not performed at the EXIT visit. Samples will be analysed at a central laboratory. PK assessment will also be used to determine belimumab concentration in confirmed positive immunogenicity samples.

6.7. Pharmacogenetic Research

Collect a blood sample for pharmacogenetics (PGx) from consenting subjects except those recruited from Study BEL114333 (who have already provided a sample as part of that study). Samples for PGx must be drawn **prior** to dosing as appropriate.

Information regarding PGx research is included in [Appendix 6](#).

7. DATA MANAGEMENT

For this study subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Originally a total of approximately 135 subjects (50 in the treatment holiday group, 50 in the control group, and 35 in the long term discontinuation group) were planned to be enrolled in this study. After 36 months had elapsed since study start, a reduction in sample size was agreed to with regulatory authorities, and a total of at least 71 patients (at least 10 in treatment holiday, at least 26 in the control group and 35 in the long term discontinuation group) will be the target sample size to be enrolled in this study. The total sample size is based on practical considerations on the availability of subjects from other ongoing belimumab studies, rather than on statistical considerations. Since this is a non-randomized study, results will be descriptive only, and not intended to be inferential. No power calculations were made in the determination of sample size for this study. However, the total of subjects is expected to provide adequate information to characterize time to SLE flare. [Table 4](#) shows the flare rates for the pooled BLISS studies.

Table 4 Flare Rates from Pooled BLISS Studies

ISE Table	Analysis	Placebo	1 mg/kg	10 mg/kg
T57	Percentage of Subjects with Flare Over 52 Weeks	81.5%	74.6%	74.6%
TAC411	Percentage of Subjects with Flare Over 52 Weeks Post Week 24	68.5%	54.7%	57.5%
TAC613	Percentage of Subjects with Flare Over 52 Weeks Among SRI Wk 52 Responders	73.4%	69.8%	67.4%

8.1. Data Analysis Considerations

8.1.1. Analysis Populations

The primary analysis population will be the Intent-to-treat (ITT) population. The ITT population will consist of all subjects enrolled in the study.

8.1.2. Primary Efficacy Analysis

Time to first SLE flare will be analyzed using a time-to-event analysis. Time to first SLE flare is defined as the number of days from Day 0 of the BEL116027 study to the first occurrence of a SLE flare. If a subject withdraws from the study or completes week 52 without a SLE flare, time to the first SLE flare will be censored at the time of the last observation (last visit measuring flare). However, if a subject receives prohibited medication during the study, the subject will be considered as having a SLE flare at the time the medication is started. Data observed at or prior to the Day 0 visit will not be included in this analysis.

8.1.3. Analysis of Additional Efficacy Endpoints

For the primary analysis of the additional efficacy and biomarkers, the baseline will be defined as study Day 0 of the original parent study. Additionally, for some of the endpoints, a secondary analysis will be performed by defining the baseline as Day 0 of the BEL116027 study.

The major analysis of the additional efficacy and biomarkers will include descriptive tabulation of secondary endpoints by treatment group according to the treatment group they are assigned to in the BEL116027 study.

8.1.4. Safety Analysis

AEs will be graded for severity by the investigator using Adverse Event Severity Grading Tables ([Appendix 6](#)) or the grades in [Section 6.4.8](#), as appropriate. The frequency of AEs will be tabulated by MedDRA system organ class and preferred term and by treatment groups, according to the treatment group that the subjects were assigned to in the BEL116027 study. Additional analysis may be performed based on event rates adjusting for subject-years on study agent. The number of subjects with AEs and the incidence rate of AEs will be summarised in each 6-month time interval. AEs will also be summarised by MedDRA SOCs and preferred terms for those that are considered to be at least possibly related to study agent and those that are considered to be severe (Grade 3 and Grade 4). Discontinuations due to AEs will be summarised.

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 Grade 4 laboratory abnormalities will be summarised.

Immunogenicity (anti-belimumab antibodies) will be summarized at baseline and during treatment and follow-up.

8.1.5. Pharmacokinetic Analysis

Serum belimumab concentration will be determined by an ECL-based immunoassay. Results for this study will be presented using appropriate graphic and tabular summaries.

8.1.6. Interim Analysis

An interim analysis of the data in this trial may be performed to support a submission to regulatory authorities relating to marketing authorization (e.g., to summarize and submit this long term safety data to regulatory authorities in the initial BLA and other marketing authorization submissions). Additional interim analyses may be required to support subsequent safety updates to regulatory authorities.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

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

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study. Obtain written informed consent from all subjects to participate in this study at the Screening visit.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described in [Appendix 6](#), unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include

identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.5. Study and Site Closure

Subjects recruited into this study will continue to receive treatment with belimumab until such time as belimumab becomes commercially available in Northeast Asia, or the subject elects to participate in another belimumab continuation study for SLE, or the Sponsor discontinues the maintenance phase of the study for China subjects with the provision for China subjects to elect to participate in a different protocol to continue to receive belimumab, or until either the subject's physician withdraws the subject from the study, or upon the decision by the sponsor to discontinue the study. Safety reporting will be as specified in the protocol the subject participates in. Upon completion of treatment, every effort should be made to evaluate subjects for Week 16 post-treatment follow-up visit and the 6-month post-treatment visit. Once all reasonable efforts have been made, the study will be considered complete/terminated.

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

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

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

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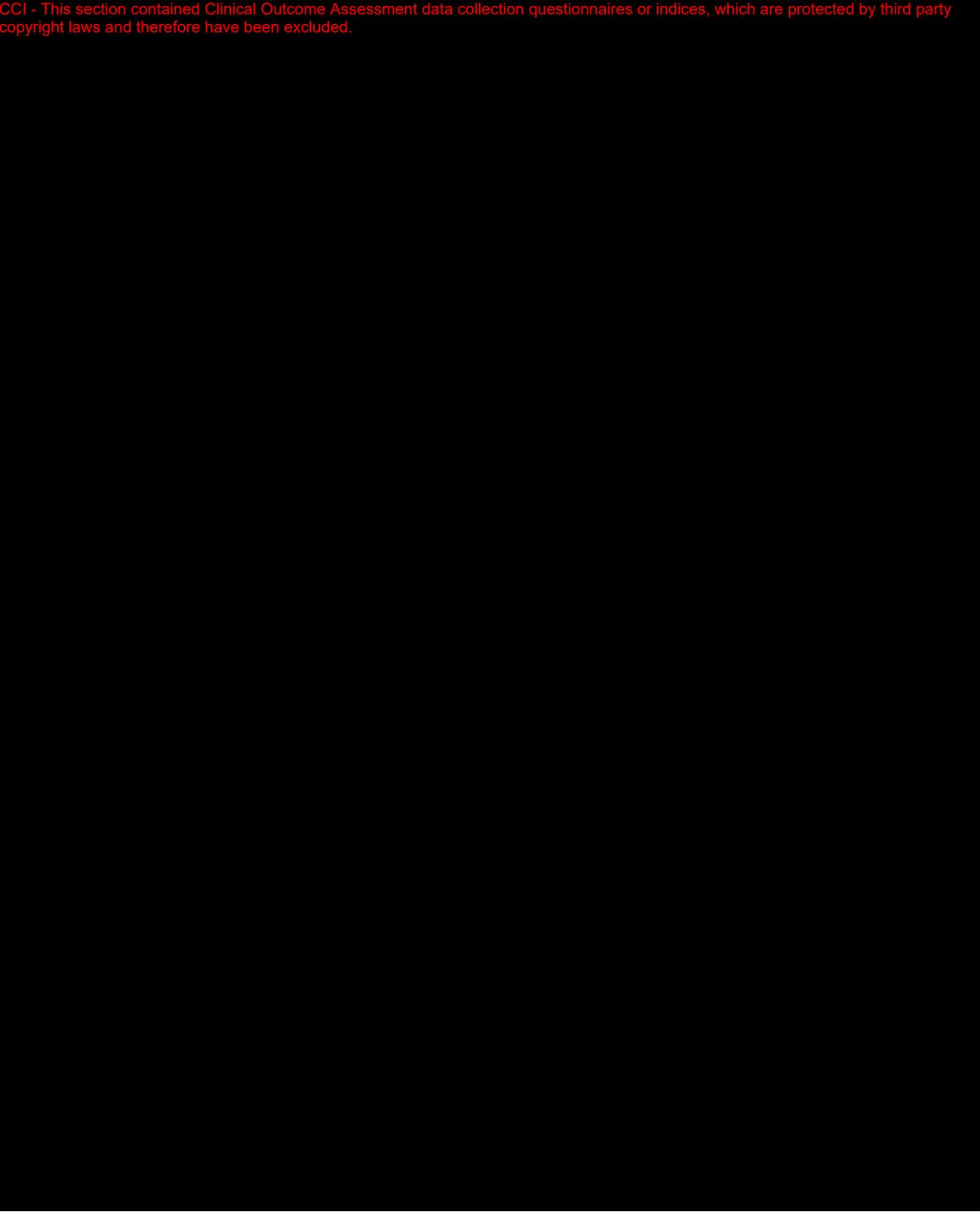
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11. APPENDICES

11.1. Appendix 1: SELINA 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.



SELENA SLEDAI Disease Assessment Scales (continued)

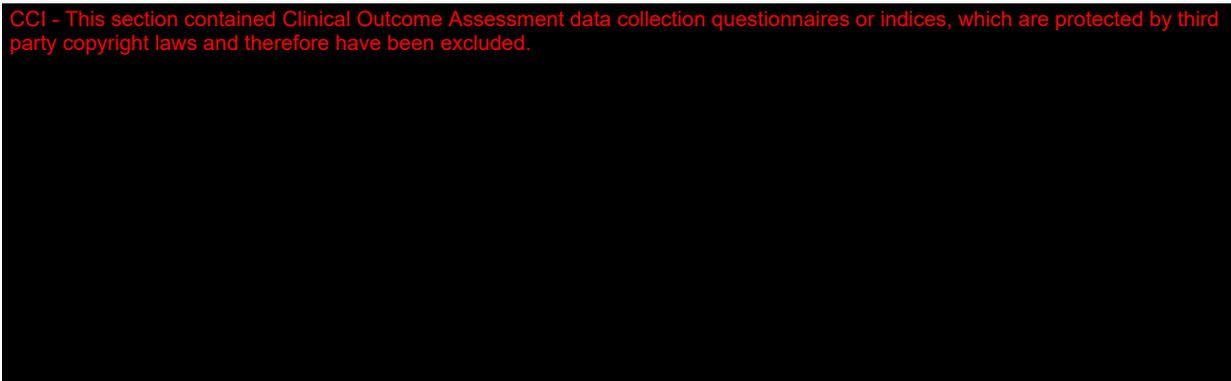
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



SELENA SLEDAI Disease Assessment Scales (continued)

Physician's Global Disease Assessment

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



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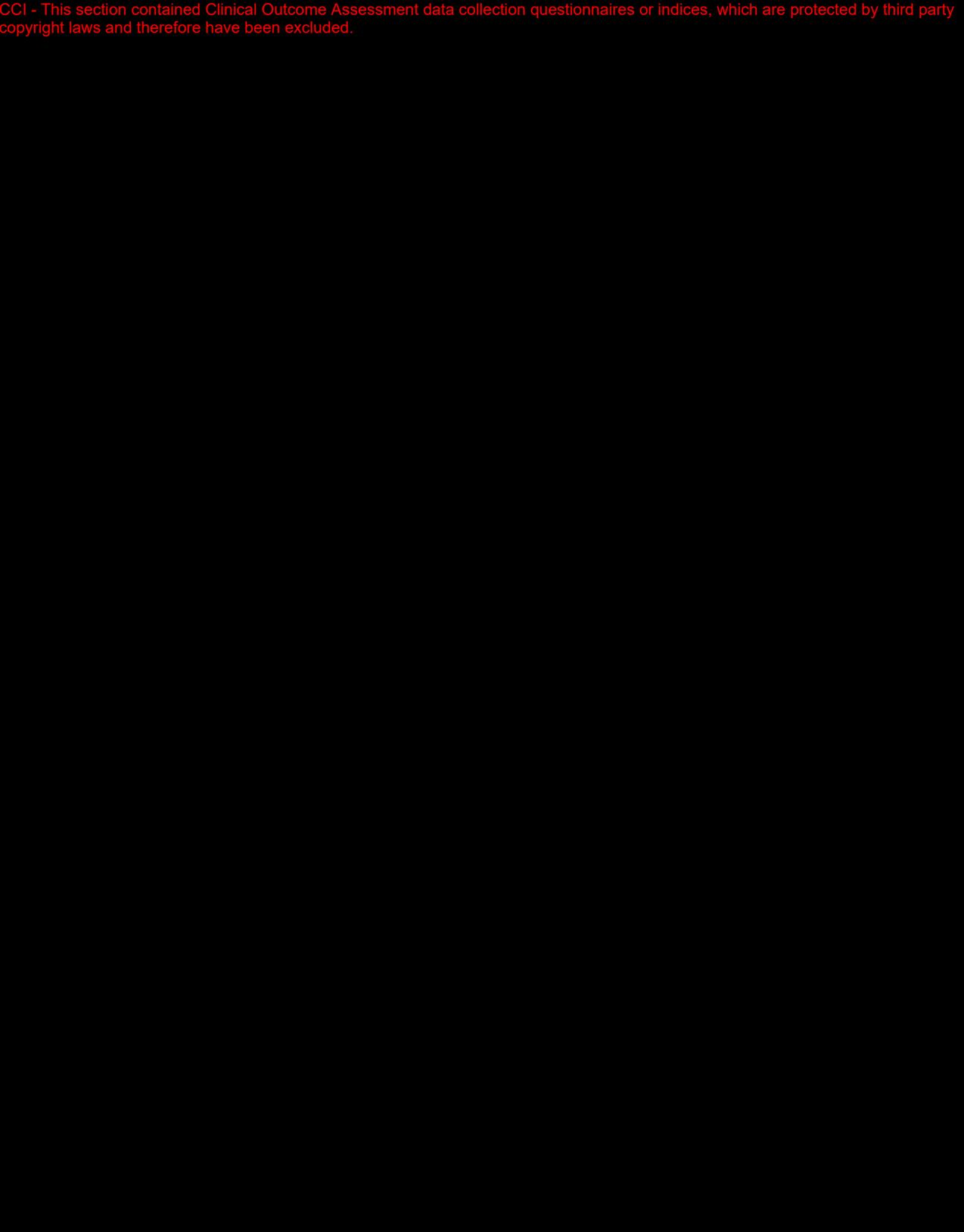
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11.2. Appendix 2: SLICC/ACR Damage Index

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.



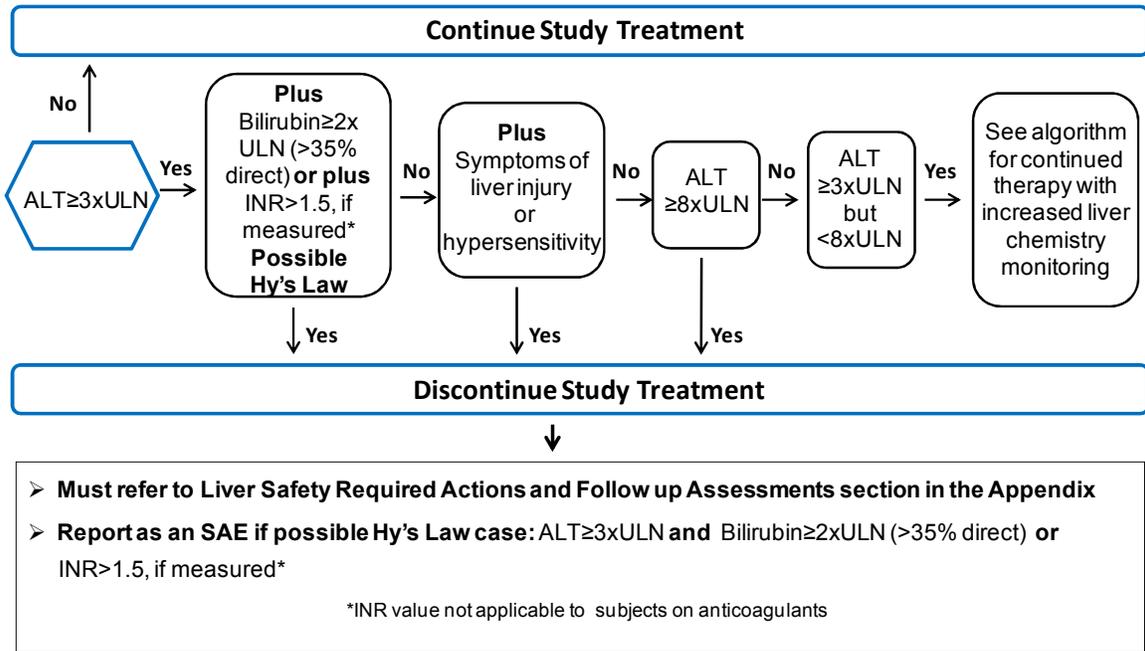
SLICC/ACR Damage Index (continued)**References**

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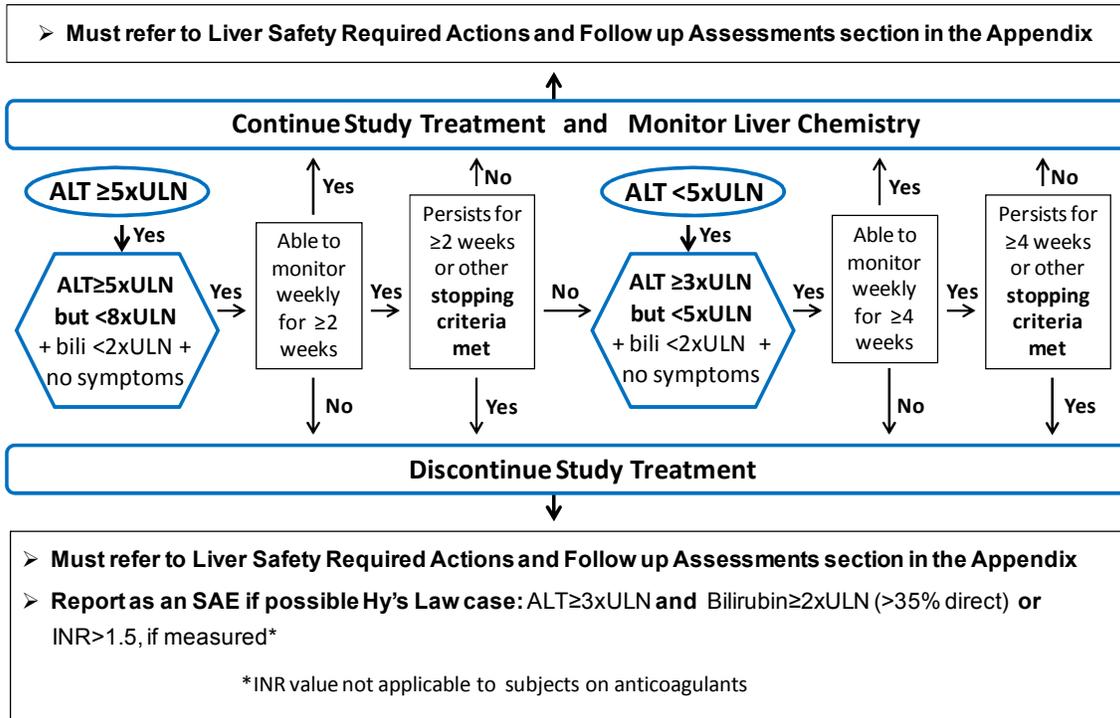
11.3. Appendix 3: Liver Chemistry Stopping and Followup Criteria

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



- Liver Safety Required Actions and Follow up Assessments Section can be found in Section [6.4.1](#).

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 Section 6.4.1.

11.4. Appendix 4: Adverse Event and Laboratory Value Severity Grade Tables

<u>HEMATOLOGY</u>	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	<u>MILD</u>	<u>MODERATE</u>	<u>SEVERE</u>	<u>POTENTIALLY LIFE-THREATENING</u>
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/mm ³	2000-2999/mm ³	1000-1999/mm ³	< 1000/mm ³
Absolute Neutrophil Count	1500-1999/mm ³	1000-1499/mm ³	500-999/mm ³	< 500/mm ³
Platelets	75,000 - 99,999/mm ³	50,000 – 74,999/mm ³	25,000 - 49,999/mm ³	< 25,000/mm ³
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

Appendix 4: Adverse Event and Laboratory Value Severity Grade Tables (continued)

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
<u>CARDIOVASCULAR</u>	<u>MILD</u>	<u>MODERATE</u>	<u>SEVERE</u>	<u>POTENTIALLY LIFE-THREATENING</u>
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

Appendix 4: Adverse Event and Laboratory Value Severity Grade Tables (continued)

CHEMISTRIES	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	MILD	MODERATE	SEVERE	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

Appendix 4: Adverse Event and Laboratory Value Severity Grade Tables (continued)

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
<u>CHEMISTRIES (continued)</u>	<u>MILD</u>	<u>MODERATE</u>	<u>SEVERE</u>	<u>POTENTIALLY LIFE-THREATENING</u>
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
<i>Alkaline Phosphatase</i>	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
<i>Pancreatic amylase</i>	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
<i>Lipase</i>	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
<i>Hypoglobulinemia (IgG)*</i>	550-700 mg/dL	400-549 mg/dL	250-399 mg/dL	< 250 mg/dL
(continued)				

*[Eibl, 1995; Goldfarb, 2001; Yamini, 2001].

Modified from DMID Adult Toxicity Tables, 2001

Appendix 4: Adverse Event and Laboratory Value Severity Grade Tables (continued)

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
GASTROINTESTINAL	MILD	MODERATE	SEVERE	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

Appendix 4: Adverse Event and Laboratory Value Severity Grade Tables (continued)

<u>RESPIRATORY</u>	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	<u>MILD</u>	<u>MODERATE</u>	<u>SEVERE</u>	<u>POTENTIALLY LIFE-THREATENING</u>
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

<u>URINALYSIS</u>	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	<u>MILD</u>	<u>MODERATE</u>	<u>SEVERE</u>	<u>POTENTIALLY LIFE-THREATENING</u>
Proteinuria				
<i>Dispstick</i>				
Protein	1 +	2-3 +	4 +	Nephrotic syndrome
<i>Spot Urine:</i> Protein:Creatinine Ratio mg/mg	0.2-1.0	> 1.0-2.0	> 2.0-3.5	> 3.5
<i>24 Hour Urine:</i> Protein	200 mg - 1g loss/day	> 1-2 g loss/day	> 2-3.5 g loss/day	Nephrotic syndrome OR > 3.5 g loss/day
Hematuria	Microscopic only > 3 to < 10 RBC/hpf	Gross, No clots ≥ 10 RBC/hpf	Gross plus clots OR RBC casts	Obstructive OR transfusion required
(continued)				
RBC = red blood cell; hpf = high power field.				
Modified from DMID Adult Toxicity Tables, 2001				

Appendix 4: Adverse Event and Laboratory Value Severity Grade Tables (continued)

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
<u>MISCELLANEOUS</u>	<u>MILD</u>	<u>MODERATE</u>	<u>SEVERE</u>	<u>POTENTIALLY LIFE-THREATENING</u>
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

Appendix 4: Adverse Event and Laboratory Value Severity Grade Tables (continued)

NEUROLOGIC	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	MILD	MODERATE	SEVERE	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

11.5. Appendix 5: Clinical Laboratory Tests

<u>Hematology</u>	<u>Urinalysis</u>	<u>Modified Chem-20</u>
Total white blood cell count Differential: Absolute Neutrophils Segmented Neutrophils Band Neutrophils Myelocytes Metamyelocytes Promyelocytes Lymphocytes Monocytes Eosinophils Basophils Hemoglobin Hematocrit Red blood cell (RBC) count Platelet count Prothrombin time (PT) Partial thromboplastin time (PTT)	Protein Glucose Ketones Occult blood Microscopic examination including: WBC per hpf RBC per hpf Dysmorphic RBC Casts (specified by type e.g., RBC, WBC) Spot Urine (protein : creatinine ratio) Urine Pregnancy	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 Hepatitis B Viral DNA PCR Quantitative (HBV DNA) Estimated Creatinine Clearance/ GFR (Cockcroft-Gault) Liver event follow-up assessments: Hepatitis A IgM antibody HBsAg and hep B Core antibody (IgM) Hepatitis C RNA Hepatitis delta antibody 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 PK IgG Fractionated bilirubin Serum acetaminophen
<u>Biological Markers</u>		
BLYS protein Serum complement (C3 and C4) B-cell subtypes <u>Immunoglobulins</u> Serum immunoglobulin isotypes: IgG, IgM, IgA <u>Immunogenicity</u>		
<u>Autoantibodies</u>		
ANA Anti-dsDNA aCL		

11.6. Appendix 6: Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), 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). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	<i>HLA-B*57:01</i> (Human Leukocyte Antigen B)	Carriage of the <i>HLA-B*57:01</i> variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective <i>HLA-B*57:01</i> screening and exclusion of <i>HLA-B*57:01</i> positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective <i>HLA-B*57:01</i> screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. <i>HLA-B*57:01</i> screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia Chung, 2010; Ferrell, 2008	<i>HLA-B*15:02</i>	Independent studies indicated that patients of East Asian ancestry who carry <i>HLA-B*15:02</i> are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of <i>HLA-B*15:02</i> prior to initiating treatment with carbamazepine.

Drug	Disease	Gene Variant	Outcome
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	<i>UGT1A1*28</i>	Variations in the <i>UGT1A1</i> gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular <i>UGT1A1</i> gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the <i>UGT1A1*28</i> variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

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

Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to belimumab.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and 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, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Pharmacokinetics and/or pharmacodynamics of study treatment
- Safety and/or tolerability
- Efficacy

Study Population

Any subject who is enrolled in the clinical study, can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Blood samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

If taking blood samples: in addition to any blood samples taken for the clinical study, a whole blood sample (~6 ml) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

- The PGx sample is labelled (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 is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may 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 a set of studies) of belimumab has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to belimumab.

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

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

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the PGx sample, if already collected:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent for 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 GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample

Destruction Request Form to GSK as directed on the form. This can be done at any time when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

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 should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, 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.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

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.

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

GSK may summarize the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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11.7. Appendix 7: Country Specific Requirements

The following sections were changed in country-specific Protocol Amendment 01 for China and all China sites and these changes continue to **apply only to China and all China sites**. [Appendix 8](#) provides the list of changes made in Protocol Amendment 01.

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Amendment 01, PROTOCOL SUMMARY, Study Design

A phase IV, multi-centre, open-label, non-randomized, efficacy and safety study (including potential rebound) of:

- the effect of temporary discontinuation of belimumab 10 mg/kg therapy for 24 weeks and reintroduction of belimumab 10 mg/kg therapy for 28 weeks plus standard of care (referred to as ‘treatment holiday’) in subjects with low SLE disease activity.
- rebound phenomenon in subjects who have discontinued belimumab therapy (stratified by SLE disease activity, SELENA SLEDAI score ≤ 3 or SELENA SLEDAI score >3).

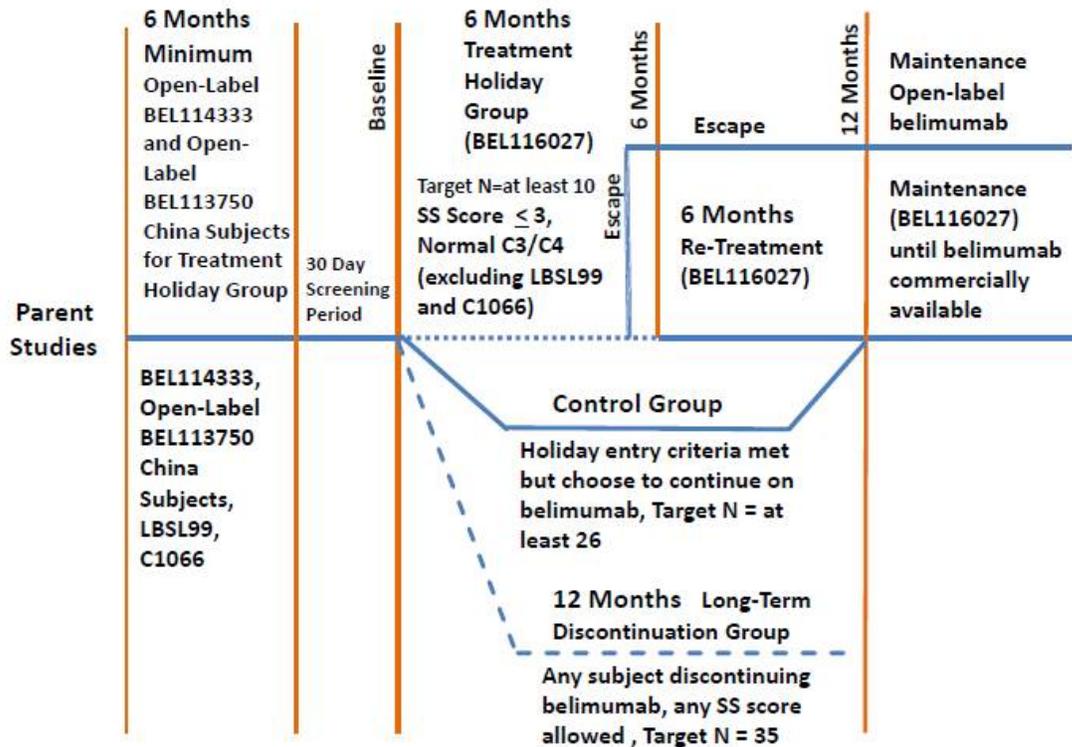
The study consists of a screening phase of up to 30 days, a 52-week treatment/observation phase with an escape option, a maintenance phase, and a follow-up phase. The study consists of a treatment holiday group, a control group, and a long-term discontinuation group. All 3 subject groups will be recruited from the BEL114333 continuation study of belimumab in SLE, and from the open-label (OL) period BEL113750 for China subjects. Additionally, subjects in the long-term discontinuation group will also be recruited from the HGS1006-C1066 and LBSL99 continuation studies of belimumab in SLE. All subjects will be assessed every 4 weeks for 52 weeks. After 52 weeks, eligible subjects in the treatment holiday and control groups have the option to continue receiving belimumab therapy in the maintenance phase of this study. Two follow-up visits are scheduled for subjects in the treatment holiday and control groups who are prematurely withdrawn from the study. Subject completion for subjects in the treatment holiday group is defined as completion of the 24-week treatment holiday period plus the belimumab re-introduction treatment period to Week 52. Subject completion for subjects in the control and long-term discontinuation groups is defined as completion of all visits to Week 52.

Amendment 01, Section 3.1 Investigational Plan, Study Design

A phase IV, multi-centre, open-label, non-randomized, efficacy and safety study (including potential rebound) of:

- the effect of temporary discontinuation of belimumab 10 mg/kg therapy for 24 weeks and reintroduction of belimumab 10 mg/kg therapy for 28 weeks plus standard of care (referred to as ‘treatment holiday’) in subjects with low SLE disease activity (Figure 1).
- rebound phenomenon in subjects who have discontinued belimumab therapy (Figure 1).

Amendment 01, Figure 1 Study Schematic



Subjects will be recruited from 3 open-label continuation studies of belimumab in SLE, and from the open-label (OL) period of BEL113750 for China subjects. This study will comprise 3 distinct groups of subjects as outlined below:

- Treatment Holiday group:** This group will be used to assess the effect of temporary discontinuation (including rebound phenomenon) and re-introduction of belimumab 10 mg/kg therapy. These subjects will be recruited from the BEL114333 belimumab continuation study in subjects with SLE, and from the open-label period of BEL113750 for China subjects. Subjects will have been treated with belimumab for at least 6 months and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal. The target enrolment for this group is at least 10 subjects.
- Treatment Control group:** This group will serve as a control to the treatment holiday group. These subjects will be recruited from the BEL114333 belimumab continuation study in subjects with SLE, and from the open-label period of BEL113750 for China subjects. Subjects will have been treated with belimumab for at least 6 months and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal but will continue their current treatment with belimumab 10 mg/kg. The target enrolment for this group is at least 26 subjects.

- **Long-term Discontinuation group:** This group will also be used to assess rebound phenomenon in SLE subjects who have discontinued therapy with belimumab 10 mg/kg and are expected to remain off belimumab therapy for at least 12 months but remain on standard of care therapy. These subjects will be recruited from 3 belimumab open-label continuation studies in subjects with SLE (BEL114333; HGS1006-C1066; LBSL99), and from the open-label period of BEL113750 for China subjects. Subjects will have been treated with belimumab for at least 6 months in one of these continuation studies and from the open-label period of BEL113750 for China subjects for at least 6 months, but will have withdrawn from belimumab therapy for no longer than 8 weeks prior to entry into this study. These subjects may have any level of SLE disease activity. The target enrolment for this group is 35 subjects.

The study consists of a screening phase of up to 30 days, a 52-week treatment/observation phase with an escape option, a maintenance phase, and a follow-up phase. The screening phase will allow an assessment of the SELENA SLEDAI score and complement (C3 and C4) levels as part of the eligibility criteria for subjects in the treatment holiday and control groups. All subjects will attend clinic visits for efficacy and safety assessments every 4 weeks for 52 weeks. At the end of the 52 week period, subjects in the treatment holiday and control groups will have the option to continue belimumab therapy in the maintenance phase of this study only if belimumab is not commercially available in a subject's country of participation. This maintenance phase will last until such time as belimumab becomes commercially available in a subject's country of participation, or the Sponsor discontinues the maintenance phase of the study for China subjects with the provision for China subjects to elect to participate in a different protocol to continue to receive belimumab, or the Sponsor decides to terminate the study. Safety reporting will be as specified in the protocol the subject participates in.

A 16-week follow-up visit will be scheduled for subjects in the treatment holiday and control groups after the withdrawal visit or the last dose of belimumab as appropriate. Additionally, a 6 month follow-up visit is required for those subjects in the treatment holiday or control groups.

Subjects in the treatment holiday group may re-start belimumab therapy prior to Week 24 in the event of a severe SLE flare as per the SLE flare index ([Appendix 1](#)). These subjects will then enter the maintenance part of this study by the escape option for ongoing belimumab treatment.

Subject completion for subjects in the treatment holiday group is defined as completion of the 24-week treatment holiday period plus the belimumab re-introduction treatment period to Week 52. Subject completion for subjects in the control and long-term discontinuation groups is defined as completion of all visits to Week 52.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

Amendment 01, Section 3.2 Discussion of Design

This study proposes to recruit subjects from 3 ongoing open-label continuation studies of belimumab in SLE subjects as well as from the open-label period of BEL113750 for China subjects in order to obtain an eligible population in the shortest timeframe:

- BEL114333: A Phase III open-label continuation of parent study BEL113750, which is an ongoing Phase III, double-blind, placebo-controlled study of belimumab in SLE subjects conducted in Japan and South Korea.
- BEL113750: Only China subjects from the open-label portion of this Phase III, randomized, parallel group, double-blind study to evaluate the efficacy and safety of 10mg/kg belimumab intravenously at Weeks 0, 2, and 4, and then every 4 weeks, compared with placebo over a 52-week treatment period in subjects with active systemic lupus erythematosus (SELENA SLEDAI score ≥ 8) in Northeast Asia.
- HGS1006-C1066: An ongoing Phase III, open-label continuation study of parent study HGS1006-C1056 (BLISS 76), which enrolled and treated 268 SLE subjects with belimumab conducted in the United States
- LBSL99: An ongoing Phase II, open-label continuation study of parent study LBSL02, which enrolled and treated 296 SLE subjects with belimumab conducted in the United States and Canada.

Subjects eligible for inclusion in the treatment holiday group will have been treated with belimumab for at least 6 months in BEL114333 or for at least 6 months in the BEL113750 open-label period for China subjects, and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal.

Subjects eligible for inclusion in the control group will have been treated with belimumab for at least 6 months in BEL114333 or for at least 6 months in the BEL113750 open-label period for China subjects, and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal but elect to continue their current treatment with belimumab 10 mg/kg.

Subjects eligible for inclusion in the long-term discontinuation group may have any level of SLE disease activity; will have been treated with belimumab for at least 6 months in any of the 3 continuation studies mentioned above, or for at least 6 months in the BEL113750 open-label period for China subjects; have discontinued belimumab therapy for no longer than 8 weeks prior to entry into this study and intend to remain off

belimumab treatment for the 12 months of this study but to remain on standard of care therapy.

Subjects eligible for inclusion in the treatment holiday group will not be recruited from the long-term continuation studies LBSL99 or HGS1006-C1066, due to regulatory commitments for completing 10 years and 5 years on treatment, respectively. However, subjects who discontinue belimumab treatment in studies LBSL99 or HGS1006-C1066 can be recruited into the long-term discontinuation group in the present study.

For subjects entering the study, a minimum of 6 months previous participation in an open-label continuation studies or China subjects in BEL113750 receiving open-label belimumab for at least 6 months, will provide subjects initially randomized to placebo in parent studies with the opportunity to reach sufficient biological activity to achieve a belimumab pharmacological and/or clinical response.

The target sample size of at least 10 subjects in the treatment holiday group and at least 26 subjects in the control group is based on estimates of subject eligibility and number of subjects from continuation study BEL114333 and China subjects in BEL113750 receiving open-label belimumab for at least 6 months, is anticipated to provide consent to participate in this study. The target sample size of 35 subjects for the long-term discontinuation group is based on practical considerations of numbers of subjects anticipated to drop-out and not on statistical considerations.

Enrolment of subjects from the 3 belimumab continuation studies or from the open-label period of BEL113750 for China subjects into the long-term discontinuation group will remain open while recruitment to the treatment holiday and control groups is ongoing or until 36 months have elapsed since study start. A target sample size of 35 subjects in the long-term discontinuation group is anticipated.

Because this study is non-randomized, subjects and investigators from study BEL114333 and China subjects and China investigators from study BEL113750 will jointly decide upon which of the three groups to enrol into. Subjects recruited from the HGS1006-C1066 and the LBSL99 studies may only choose to enter the long-term discontinuation group, as they elect to no longer receive further belimumab therapy.

Amendment 01, Section 4.2 Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the belimumab IB/IB supplement(s) and belimumab product label.

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in **all 3 subject groups** in the study must meet all of the following criteria:

1. **Belimumab therapy:** Received a minimum of 6 months therapy with belimumab 10 mg/kg in the continuation study BEL114333 or from China subjects in BEL113750 who received open-label belimumab for at least 6 months. Subjects in the long-term discontinuation group may additionally be recruited from continuation studies HGS1006-C1066 or LBSL99.
2. **Age:** 18 years of age at the Day 0 visit.
3. **Females:** A non-pregnant, non-lactating female subject is eligible to enter the study if at least one of the following conditions apply:
 - Of non-childbearing potential (i.e., women who had a hysterectomy, are postmenopausal which is defined as 1 year without menses, have both ovaries surgically removed or have current documented female sterilization procedure); or
 - Of childbearing potential (i.e., 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 urine pregnancy test at Day 0, and agree to one of the following:
 - Complete abstinence from penile-vaginal intercourse, when this is the female's preferred and usual lifestyle, for the duration of the study for subjects in the long-term discontinuation group or until 16 weeks after the last dose of belimumab for subjects in the treatment holiday and control groups; or
 - Consistent and correct use of one of the following acceptable methods of birth control for the duration of the study for subjects in the long-term discontinuation group or until 16 weeks after the last dose of belimumab for subjects in the treatment holiday and control groups:
 - Implants of etonogestrel or levonorgestrel;
 - Estrogenic vaginal ring
 - Injectable progesterone;
 - Any intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year;
 - Oral contraceptives (either combined or progesterone only);
 - Double barrier method with vaginal spermicidal agent: Condom and an occlusive cap (cervical cap/vault or diaphragm) with a vaginal spermicidal agent (foam/gel/film/cream/suppository);
 - Percutaneous 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 (e.g., barrier method).

4. **Informed consent:** Able to provide written informed consent to participate.

Additional eligibility criteria for subject enrolment in the **treatment holiday and control groups** in the study:

1. **SLE:** achieve the required minimal disease activity criteria defined as SELENA SLEDAI score ≤ 3 after a minimum of 6 months of belimumab therapy (see [Appendix 1](#) for SELENA SLEDAI).
2. **SLE Treatment:** Are on a stable SLE treatment regimen consisting of any of the following medications (alone or in combination) during the 30 day screening period prior to Day 0:
 - Corticosteroids (prednisone or prednisone equivalent)
 - Other immunosuppressive or immunomodulatory agents including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), mizoribine, calcineurin inhibitors (e.g., tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine, or thalidomide.
 - Anti-malarials (e.g., hydroxychloroquine, chloroquine, quinacrine).
 - Non-steroidal anti-inflammatory drugs (NSAIDs), including sulfasalazine.
3. **Complement:** C3 and C4 complement levels at or above the lower limit of normal of the central laboratory reference range.

Additional eligibility criteria for subject enrolment in the **control group** in the study:

1. **Belimumab therapy:** Agree to continue receiving 10mg/kg belimumab intravenous infusions every 4 weeks. Subjects must be able to receive the first dose of belimumab in **this study** 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in their **previous** continuation study, or the open-label period of BEL113750 for China subjects.

Additional eligibility criteria for subject enrolment in the **long-term discontinuation group** in the study:

1. **Continuation studies:** Voluntarily withdrawn from continuation studies BEL114333, HGS1006-C1066, LBSL99, or the open-label period of BEL113750 for China subjects, and have withdrawn from belimumab therapy for no longer than 8 weeks prior to entry into this study.

Note: investigators may stop, start, and/or change SLE medications and dosages as deemed necessary; yet long-term discontinuation subjects will remain on local standard of care SLE treatment therapy as determined by the physician during the study, or will need to be withdrawn.

Amendment 01, Section 4.3 Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in **any of the 3 subject groups** in the study:

1. **Undue risk:** Have developed clinical evidence of significant, unstable or uncontrolled, acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases), or experienced an adverse event (AE) in the belimumab continuation studies BEL114333, HGS1006-C1066, LBSL99, or in the BEL113750 open-label period for China subjects, that could, in the opinion of the principal investigator, put the subject at undue risk.
2. **Subject suitability:** Have developed any other medical diseases (e.g., cardiopulmonary), laboratory abnormalities, or conditions (e.g., poor venous access) that, in the opinion of the principal investigator, makes the subject unsuitable for the study.

Subjects meeting any of the following additional criteria must not be enrolled in the **control or treatment holiday groups** in the study:

1. **SLE:** New mild-moderate or severe flare as defined by the SLE Flare Index during the 30 day screening period prior to Day 0.
2. **Steroids:** Prednisone (or prednisone equivalent) greater than 20mg/day within the 30 day screening period.
3. **New agents:** Any new immunosuppressive/immunomodulatory agent, anti-malarial, or NSAID within the 30 day screening period prior to Day 0. However, any NSAID use for < 1 week is allowed.

Amendment 01, Section 5.1 Investigational Product and Other Study Treatment

Belimumab for intravenous (IV) infusion will be supplied in glass vials by GSK. The contents of the label will be in accordance with all applicable regulatory requirements. Detailed instructions on the preparation, administration and storage of belimumab are provided in the Pharmacy Manual. Belimumab IV solution should be prepared by a

pharmacist. Reconstitute the 400 mg single use vial of belimumab with 4.8 mL sterile water for injection to yield a final concentration of belimumab 80 mg/mL. Remove an amount of normal saline from the infusion bag equivalent to the amount of belimumab to be added, add the reconstituted belimumab, and gently invert the infusion bag to mix the solution. After reconstitution and dilution in normal saline, the material is stable for up to 8 hours at 2-8°C or at room temperature. The characteristics of belimumab are summarized in [Table 1](#).

Table 1 Belimumab Characteristics

Property	Belimumab
Formulation	Belimumab 400 mg per vial plus excipients (citric acid/sodium citrate/sucrose/polysorbate)
Dosage Form	Reconstituted solution
Unit dose strength	400 mg per vial (to contain 80 mg/mL when reconstituted with 4.8mL sterile water for injection [SWFI])
Physical description	White uniform lyophilised cake in a 20 mL vial
Manufacturer	Human Genome Sciences, Inc.
Route of administration	Intravenous

Subjects enrolled in the treatment holiday group will receive treatment with belimumab 10 mg/kg from Week 24 onwards **after** the initial 24-week treatment holiday period of the study has elapsed (see [Amendment 01, Section 3.1](#)). At the start of the belimumab reintroduction period, subjects in the treatment holiday group will receive belimumab 10 mg/kg IV infused for 1 hour every 28 days.

Subjects in the control group will receive belimumab 10 mg/kg IV infused for 1 hour every 28 days from Day 0 onwards. Subjects in this group must be able to receive their first dose of belimumab on Day 0 of this study 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the BEL114333 open-label continuation study, or after the last dose from China subjects in the open-label period of BEL113750.

Subjects in the long-term discontinuation group will not receive belimumab at any point in this study.

The dose of belimumab administered may not be altered but the rate of infusion may be slowed or interrupted if the subject appears to develop signs of adverse reaction or infusion-associated symptoms. Do **not** increase the rate of infusion above the recommended rate.

Monitor the subject 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. Trained rescue personnel and rescue medications/equipment should be available for a minimum of the first dose.

Consider administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions for subjects who have previously received intravenous immunoglobulins (IVIG) or subjects with a history of allergies (allergic responses to food, drugs, insects, or a history of urticaria). The dose of belimumab may be delayed by up to 2 weeks or the dose may be withheld if the subject experiences a clinically significant AE that, in the clinical judgement of the investigator, is possibly, probably or definitely related to belimumab, and this AE continues at the next scheduled dose, or could potentially be exacerbated by the next dose. If a similar concern is present at the time of the next scheduled dose, the investigator and Medical Monitor will discuss whether to discontinue treatment with belimumab.

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request. Belimumab should be diluted to 250 mL normal saline after reconstitution, using a typical approved plastic intravenous administration set for the infusion.

Belimumab must be stored in a secure area under the appropriate physical conditions for the product, which includes storage in a refrigerator at a temperature of 2-8°C. Maintenance of a temperature log (manual or automated) is required. Access to and administration of belimumab will be limited to the investigator and authorized site staff. Belimumab must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Destroy all used belimumab vials according to site guidelines for the destruction of investigational products, after the monitor has conducted a check of the product accountability log during the study. At the end of the study, unused belimumab vials will be destroyed on site at the study closeout visit, after the monitor has conducted final belimumab accountability and given the site approval to destroy all remaining supplies.

Amendment 01, Section 6, Time and Events Table (Year 1)

	Screen	Treatment Holiday Study														Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	--	--
Study Day	Up to -30 1	0 2	28 ±7d	56 ±7d	84 ±7d	112 ±7d	140±7d	168 ±7d	196±7d	224 ±7d	252 ±7d	280±7d	308 ±7d	336 ±7d	364 ±7d or Exit	16-wk ±7d 3	6 mo ±7d
Study Week		0	4	8	12	16	20	24	28	32	36	40	44	48	52	--	--
Written Informed Consent 4	X	X															
Demography		X															
Medical History		X															
SLE History		X															
Therapy History		X															
Physical Examination		X															
Inclusion/Exclusion		X															
Efficacy Assessments																	
DAS: SS, SLE Flare Index, PGA 5	X 1	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
SLICC/ACR Damage Index		X						X							X		
Safety Assessments																	
Vital Signs 6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight, height 6, 7		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	
Record Concurrent Medications		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	
Laboratory Assessments																	
Haematology & Modified Chem 20 (non-fasting) 6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spot urine (protein to creatinine ratio) 8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test 6, 9	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	
Pharmacogenetic Sampling 10		X															
aCL Autoantibody		X													X		

	Screen	Treatment Holiday Study														Follow-up		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	--	--	
Study Day	Up to -30 1	0 2	28 ±7d	56 ±7d	84 ±7d	112 ±7d	140±7d	168 ±7d	196±7d	224 ±7d	252 ±7d	280±7d	308 ±7d	336 ±7d	364 ±7d or Exit	16-wk ±7d 3	6 mo ±7d	
Study Week		0	4	8	12	16	20	24	28	32	36	40	44	48	52	--	--	
C3/C4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Anti-dsDNA Autoantibodies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ANA Autoantibodies		X						X							X			
IgG, IgA & IgM 11		X		X		X		X		X		X		X	X			
PT/ PTT		X																
Exploratory Lab Assessments																		
Pharmacokinetic Sampling 12		X		X		X		X 12		X					X 12			
Immunogenicity 6, 13		X			X		X 13	X		X					X	X	X 13	
BlyS Protein 14						X		X		X								
B cell Markers 15		X		X		X		X		X		X			X		X	
Investigational Product (IP)																		
IP Administration 16		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

DAS = disease activity scales; SS = SELENA SLEDAI; SLE = systemic Lupus Erythematosus; PGA = Physician's Global Assessment; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology; ALT = alanine aminotransaminase; AST = aspartate aminotransaminase; PT/PTT = prothrombin time/partial thromboplastin time; BlyS = B Lymphocyte Stimulator; IP = investigational product; aCL = anticardiolipin

1. A screening visit of up to 30 days prior to the Day 0 visit will be scheduled for subjects in the treatment holiday and control groups for assessment of SELENA SLEDAI score to assess eligibility.
2. The EXIT Visit in the respective feeder continuation studies and in the open-label period of BEL113750 for China subjects will serve as the Day 0 visit for all 3 subject groups in this study. Assessments covered for both this study at Day 0 and the Exit visit of the feeder continuation studies and the open-label period of BEL113750 for China subjects need only be performed once and recorded in the appropriate case report forms for each study. Subjects in the control group must be able to receive the 1st dose of belimumab on Day 0 of this study on average 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the feeder continuation study and in the open-label period of BEL113750 for China subjects.
3. The 16 week follow-up visit will occur at approximately 16 weeks after last dose of investigational product for subjects in the control group who withdraw at any time during the study but do not wish to enter the long-term discontinuation group and be followed for a further 12 months or for subjects in the treatment holiday group who withdraw from the study from Week 24 onwards (Visit 7) during the belimumab re-introduction period. The 16-week and 6 month follow-up visits do not apply to subjects in the long-term discontinuation group.
4. For subjects in the control group only, obtain written informed consent to participate in this study at the visit **prior to the last visit** in the relevant SLE feeder continuation study

and the open-label period of BEL113750 for China subjects.

5. Guidelines for scoring proteinuria for SELINA SLEDAI are provided in Section 6.3.1.1.
6. Complete assessment prior to belimumab dosing for subjects in the control group (to Week 48) and for subjects in the treatment holiday group (during Weeks 24 to 48 or earlier in the event of a flare).
7. For any subject whose weight changes by more than 5% from that recorded at Day 0, use the weight at the current visit for calculating the belimumab dose to be administered. Height measured only at Day 0.
8. A 24-hour urine may be done as an additional assessment if clinically indicated (e.g., renal flare).
9. Urine pregnancy test results for women of child-bearing potential must be available prior to dosing (during Weeks 0 to 48 in the control group and during Weeks 24 to 48 or earlier in the event of a flare in the treatment holiday group). Can be performed at any time during the visit for females of child-bearing potential in the long-term discontinuation group.
10. PGx sampling from consenting subjects recruited from all studies except from study BEL114333 and except from the open-label period of BEL113750 for China subjects. PGx informed consent must be obtained prior to sampling.
11. Serum immunoglobulin isotypes: IgG, IgM, IgA.
12. Pharmacokinetic sampling at select sites for subjects in the control and treatment holiday groups; subjects in the treatment holiday group can have PK sampling performed at any time during the visit between Weeks 0 and 16. Otherwise, if on a dosing day, sampling must be performed **prior** to dosing. Collect blood samples pre-dose and post-dose at the end of the infusion at Weeks 24 and 52 (or earlier if belimumab is re-started before Week 24 in the event of a severe flare by using the escape option). Subjects in the long-term discontinuation group will have one PK sampling performed at any time during the visit between Weeks 0 and 24. PK sampling for the long-term discontinuation group is not performed after Week 24.
13. Blood sample for immunogenicity will be taken at Weeks 12, 24, 36 and 52 for all three groups. In addition, a blood sample for immunogenicity will also be taken **4 weeks prior** to the reintroduction of belimumab (at Week 20 since belimumab will be reintroduced at Week 24) in the treatment holiday group. A blood sample for immunogenicity must be taken at least 6 months after the final dose of investigational product for any subjects in the control group or treatment holiday group who had an anti-belimumab antibody response at the 16-week follow-up visit (or at the last immunogenicity assessment if 16-week follow-up is not available). **Note** that serum samples for immunogenicity must be collected pre-dose at the time of dosing from subjects in the treatment holiday group who experience a severe flare prior to Week 24 and consequently receive open-label belimumab as rescue. Immunogenicity blood sample will not be collected at the 6-month follow up visit for subjects in the long-term discontinuation group as this visit does not apply to this subject group.
14. Measured in treatment holiday group at Weeks 16 and pre-dose at Week 24. Measured in long-term discontinuation group at Weeks 16, 24 and 32. Not measured in control group.
15. Biological Markers include FACS of peripheral lymphocytes: B lymphocytes (CD20+, CD20+/27+ memory, CD20+/27- naïve, CD20+/69+ activated, CD20+/138+ plasmacytoid, CD19+/27BRIGHT/38BRIGHT SLE subset and CD20-/138+ plasma cells). Note: B cell markers will not be collected at the 6-month follow up visit for subjects in the long-term discontinuation group as this visit does not apply to this subject group.
16. Only subjects in the control group will receive belimumab 10 mg/kg during Weeks 0 through 20 inclusive; subjects in the control group must be able to receive the **first** dose of belimumab **in this study** 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in their **previous** open-label continuation study. Subjects in the control group and treatment holiday groups will receive belimumab from Weeks 24 through 48 although subjects in the treatment holiday group may be treated with belimumab **prior** to Week 24 as determined by the investigator in the event of increased SLE activity. When belimumab therapy is re-started, subjects in the treatment holiday group will remain under clinical supervision for 3 hours after completion of the first 2 infusions. At the **Week 52** visit, only subjects in the treatment holiday and control groups who are continuing belimumab therapy beyond this time will be dosed.

Amendment 01, Section 6.1.2 Secondary Endpoints

The secondary endpoints are:

- Rate of any SLE Flare Index flares.
- Time to first severe SLE Flare Index flare.
- Number of subjects in the treatment holiday and long-term discontinuation group with evidence of rebound (defined as a SELENA SLEDAI score during the first 24 weeks that exceeds the baseline SELENA SLEDAI score in the original parent study).
- Number of subjects with confirmed true positive belimumab anti-drug antibodies (ADA) by the end of the study.
- Percentage change from baseline in:
 - Total serum immunoglobulin (IgG, and other isotypes: IgM and IgA)
 - Autoantibodies (anti-dsDNA, ANA), and complement (C3, C4)
- Percent change in absolute B cell subsets (CD20+, CD20+/27+ memory, CD20+/27- naïve, CD20+/69+ activated, CD20+/138+ plasmacytoid, CD19+/27BRIGHT/38BRIGHT SLE subset and CD20-/138+ plasma cells) at Weeks 0, 8, 16, 24, 32, 40 and 52 and from Weeks 24 to 52.
- Absolute change in SELENA SLEDAI score.
- Number of days of daily prednisone dose ≥ 7.5 mg/day and/or increased by 25% from Day 0 of this study to Week 24, from Day 0 of this study to Week 52, and from Week 24 to Week 52.
- Number of days of daily prednisone dose ≤ 7.5 mg/day and/or decreased by 25% from Day 0 of this study to Week 24, from Day 0 of this study to Week 52, and from Week 24 to Week 52.

Note: baseline is the time before any treatment with belimumab, which was Day 0 of the original parent studies that fed into the 3 continuation studies, and Day 0 of the blinded period of BEL113750 for China subjects, from which subjects were recruited into this study. When Day 0 is used in relation to endpoints, this refers to Day 0 of this study.

Amendment 01, Section 6.2 Critical Baseline Assessments

The screening phase of up to 30 days will allow an assessment of the SELENA SLEDAI score as part of the eligibility criteria for subjects in the treatment holiday and control groups.

The EXIT visit of the relevant SLE continuation protocol ((BEL114333, HGS1006-C1066, or LBSL99), or the open-label period of BEL113750 for China subjects, from which the subject is recruited will serve as the Day 0 visit in this study. Subjects in the control group will be dosed with belimumab at the Day 0 visit as part of this protocol. These subjects must be able to receive the Day 0 dose in this study 4 weeks (minimum of

2 weeks, maximum of 8 weeks) after the last dose in the previous open-label continuation study, or the open-label period of BEL113750 for China subjects. Any procedures from this protocol or from the relevant previous open-label continuation protocols, or the open-label period of BEL113750 for China subjects to be performed pre-dose must be completed before dosing subjects in the control group. Subjects in the control group should sign the informed consent to participate in this study at the visit immediately prior to the EXIT visit to ensure a supply of belimumab for the Day 0 visit in this study. Subjects in the treatment holiday and long-term discontinuation groups should sign the informed consent at the screening visit and Day 0 visit, respectively of this study.

Procedures necessary for the Day 0 visit of this protocol and for the last visit of the relevant SLE open-label continuation protocol, or the open-label period of BEL113750 for China subjects, from which the subject is recruited need only be performed once. Results from Day 0 procedures that are duplicated in the relevant SLE continuation study will be recorded in the eCRF for that study and must also be **transcribed** to the relevant eCRFs in this study. Additional Day 0 procedures exclusive to this study will be recorded directly in the eCRFs for this study.

Amendment 01, Section 6.3.1.1 SELENA SLEDAI Score

The SELENA SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) used in this study is a slightly modified version of the SLEDAI developed for a National Institutes of Health sponsored multicentre study of estrogen/progesterone hormone use in women with SLE [Buyon, 2005; Petri, 2005]. The descriptions for some of the items are slightly modified, but the organ systems and weighted scores are the same as the published SLEDAI.

The SLEDAI is a validated index for assessing SLE disease activity [Bombardier, 1992]. It is a weighted index in which signs and symptoms, laboratory tests, and physician's assessment for each of 9 organ systems are given a weighted score and summed, if present at the time of the visit or in the preceding 10 days:

- Score of 8 each for CNS and vascular items.
- Score of 4 each for renal and musculoskeletal items.
- Score of 2 each for serosal, dermal, and immunologic items.
- Score of 1 each for constitutional and hematologic items.

The maximum theoretical score for the SELENA SLEDAI is 105 (all 24 descriptors present simultaneously) with 0 indicating inactive disease. A copy of the index is provided in [Appendix 1](#).

Completion of the index requires collection of a 24-hour urine sample for assessment of proteinuria (although spot urine protein:creatinine ratio is commonly substituted in

practice), measurement of anti-dsDNA, C3, C4, haematology, and urinalysis, and for subjects with myositis, CPK.

However, spot urine protein:creatinine ratio will be used for determining proteinuria for the SELENA SLEDAI in this study since there is a strong correlation between the protein content of a 24-hour urine collection and the protein:creatinine ratio in a single urine sample [[Ginsberg, 1983](#); [Ruggenti, 1998](#); [Clinical Practice Guidelines for Chronic Kidney Disease, 2002](#); [Price, 2005](#)].

Scoring for proteinuria in the SELENA SLEDAI disease activity index will be in accordance with the following guidelines.

Scoring for Proteinuria at Screening for Eligibility

The proteinuria score for SELENA SLEDAI must be 0 at the most recent assessment performed in BEL114333 or in the open-label period of BEL113750 for China subjects. If at the screening visit the assessment of 24-hour proteinuria (by spot urine protein to creatinine ratio) shows >0.5 g/24 hour equivalent increase above the previous value (in BEL114333) or the subject develops new onset of proteinuria >0.5 g/24 hour equivalent, 4 points will be assigned at the screening assessment.

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 (i.e., baseline), the subject, by default, will have an improving SELENA SLEDAI score. 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:

- **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 urine protein to 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.

- **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 (i.e., 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.

Amendment 01, Section 6.3.1.2 Laboratory tests for SELENA SLEDAI

A strong correlation has been demonstrated between the protein content of a 24-hour urine collection and the protein:creatinine ratio in a single urine sample [Ginsberg, 1983; Ruggenti, 1998; [Clinical Practice Guidelines for Chronic Kidney Disease](#), 2002; Price, 2005]. For this reason, spot urine protein:creatinine ratio will be used for determining proteinuria in this study for the SELENA SLEDAI 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 [[Clinical Practice Guidelines for Chronic Kidney Disease](#), 2002]. Therefore, GFR estimated by the Cockcroft-Gault formula will be used as was done in the Phase II trial of belimumab (LBSL02) and Phase III.

Cockcroft-Gault Equation [[Cockcroft](#), 1976]

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

Values outside the reference laboratory normal range require the investigator's assessment of relationship to SLE.

Amendment 01, Section 6.4.1.1 Liver Chemistry Stopping and Follow up Criteria, Additional Hepatitis B Monitoring

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

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

Amendment 01, Section 6.7 Pharmacogenetic Research

Collect a blood sample for pharmacogenetics (PGx) from consenting subjects except those recruited from Study BEL114333 and except from the open-label period of BEL113750 for China subjects (who have already provided a sample as part of that study). Samples for PGx must be drawn prior to dosing as appropriate.

Information regarding PGx research is included in [Appendix 6](#).

Amendment 01, Appendix 5: Clinical Laboratory Tests

The changes made to this section during Amendment 01 (i.e., adding Hepatitis B Viral DNA PCR Quantitative (HBV DNA), BLyS Protein, ANA, aCL) are now incorporated into [Appendix 5](#) as part of Global Amendment 02. See current [Appendix 5](#).

11.8. Appendix 8: Protocol Changes

Protocol Amendment 06

Protocol amendment 06 applies to all countries and sites.

Description of Changes

Changes are highlighted in **bold**.

Change 1: SPONSOR INFORMATION PAGE

Change from:

Backup Medical Monitor

PPD [REDACTED] DO (Director, Immuno-Inflammation Medicine Development Center)

Tel: PPD [REDACTED]

Mobile: PPD [REDACTED]

To:

Backup Medical Monitor

See Study Reference Manual for Contact Information

Rationale: Update location of contact information for Backup Medical Monitor.

Change 2: Protocol Summary Study Design

Change from:

All 3 subject groups will be recruited from the BEL114333 continuation study of belimumab in SLE.

To:

All 3 subject groups will be recruited from the BEL114333 continuation study of belimumab in SLE and **as described in Appendix 11.7, from the open-label (OL) period BEL113750 for China subjects.**

Rationale: Provide clarification on Appendix 11.7, recruitment from open-label BEL113750 for China subjects.

Change 3: Section 3.1 Study Design

Change from:

Subjects will be recruited from 3 open-label continuation studies of belimumab in SLE. This study will comprise 3 distinct groups of subjects as outlined below:

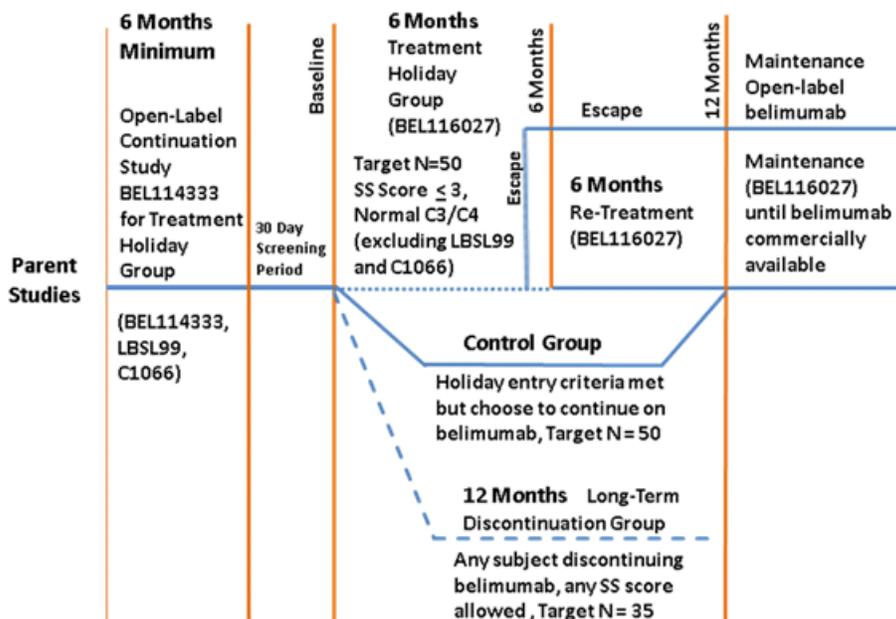
To:

Subjects will be recruited from 3 open-label continuation studies of belimumab in SLE. **See Appendix 11.7 for recruitment from the open-label (OL) period BEL113750 for China subjects.** This study will comprise 3 distinct groups of subjects as outlined below:

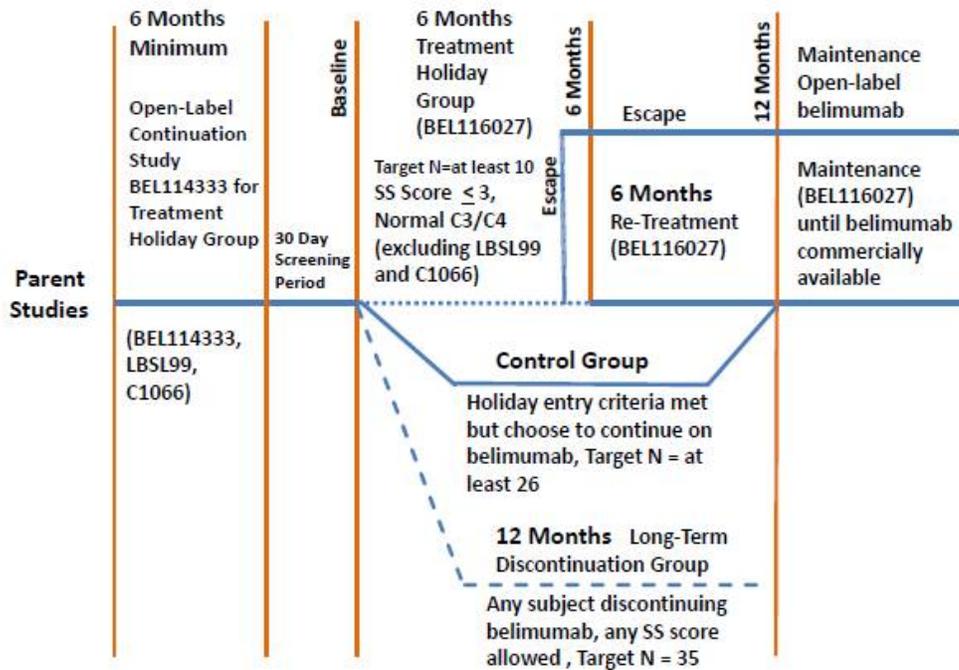
Rationale: Provide clarification on Appendix 11.7, recruitment from open-label BEL113750 for China subjects.

Change 4: Section 3.1 Study Design, Figure 1

Change from:



To:



Rationale: Updated figure for changes in target sample size as agreed upon with the EMA.

Change 5: Section 3.1 Study Design

Change from:

- **Treatment Holiday group:** The target enrolment for this group is 50 subjects.
- **Treatment Control group:** The target enrolment for this group is 50 subjects.

To:

- **Treatment Holiday group:** The target enrolment for this group is **at least 10** subjects.
- **Treatment Control group:** The target enrolment for this group is **at least 26** subjects.

Rationale: Updated text for changes in target sample size as agreed upon with the EMA.

Change 6: Section 3.1 Study Design

Change from:

A 16-week follow-up visit will be scheduled for subjects in the treatment holiday and control groups who withdraw prior to Week 52. Additionally, a 6 month follow-up visit is required for those subjects in the treatment holiday or control groups **who have an anti-belimumab antibody response at the 16-week follow-up visit (or at the last immunogenicity assessment if 16-week follow-up is not available)**.

To:

A 16-week follow-up visit will be scheduled for subjects in the treatment holiday and control groups **after the withdrawal visit or the last dose of belimumab as appropriate**. Additionally, a 6 month follow-up visit is required for those subjects in the treatment holiday or control groups.

Rationale: Provides clarification of protocol wording. The sentence regarding 6-month follow-up should have been truncated prior to protocol amendment 5 publishing.

Change 7: Section 3.2 Discussion of Design

Change from:

- **BEL114333:** A Phase III open-label continuation of parent study BEL113750, which is an ongoing Phase III, double-blind, placebo-controlled study of belimumab in SLE subjects conducted in Japan, South Korea and China.

To:

- **BEL114333:** A Phase III open-label continuation of parent study BEL113750, which is an ongoing Phase III, double-blind, placebo-controlled study of belimumab in SLE subjects conducted in Japan, South Korea and China (**for China see Appendix 11.7 for country-specific requirements regarding recruitment from the open-label period of BEL113750**).

Rationale: Provide clarification on Appendix 11.7, recruitment from open-label BEL113750 for China subjects.

Change 8: Section 3.2 Discussion of Design

Change from:

The target sample size of 50 subjects in **each of** the treatment holiday and control groups is based on estimates of subject eligibility and number of subjects from continuation study BEL114333 anticipated to provide consent to participate in this study.

To:

The target sample size of **at least 10** subjects in the treatment holiday **group** and **at least 26 subjects in the control group** is based on estimates of subject eligibility and number of subjects from continuation study BEL114333 anticipated to provide consent to participate in this study.

Rationale: Updated text for changes in target sample size as agreed upon with the EMA.

Change 9: Section 4.1 Number of Subjects***Change from:***

The target sample size for subjects in the treatment holiday and control groups is 50 subjects per group. Each group will end recruitment when their target sample size **of 50 subjects** is reached. Enrolment in this study will close when the target of 50 subjects in the treatment holiday and control groups has been achieved or 36 months after study start, whichever comes first.

To:

The target sample size for subjects in the treatment holiday group is **at least 10** subjects **and in the control group, at least 26 subjects**. Each group will end recruitment when their target sample size is reached. Enrolment in this study will close when the target **number of** subjects in the treatment holiday and control groups has been achieved or 36 months after study start, whichever comes first.

Rationale: Updated text for changes in target sample size as agreed upon with the EMA.

Change 10: Section 4.4 Withdrawal Criteria***Change from:***

These subjects will complete the Week 52 Exit visit (except for dosing with belimumab) at the time of discontinuation and the 16-week follow-up visit assessments at least 16 weeks after the withdrawal visit or last dose of belimumab as appropriate (see Section 6). The 6 month follow-up visit is scheduled only for those subjects in the treatment holiday or control groups **who have an anti-belimumab antibody response at the 16-week follow-up visit**.

To:

These subjects will complete the Week 52 Exit visit (except for dosing with belimumab) at the time of discontinuation and the 16-week follow-up visit assessments at least 16 weeks after the withdrawal visit or last dose of belimumab as appropriate (see Section 6).

The 6 month follow-up visit is scheduled only for those subjects in the treatment holiday or control groups.

Rationale: Provides clarification of protocol wording. The sentence should have been truncated prior to protocol amendment 5 publishing.

Change 11: Section 6 Study Assessments and Procedures

Change from:

Subjects in the treatment holiday and control groups who meet the protocol-defined withdrawal criteria specified in Section 4.4 at any time during Year 1 or the additional years will undergo assessments scheduled at the Exit visit (Week 52) in Table 2 except for dosing with belimumab. At approximately 16 weeks after the withdrawal visit or the last dose of belimumab as appropriate, these subjects will also undergo the assessments scheduled at the 16-week follow-up visit; the 6 month follow-up visit is scheduled only for these discontinued subjects in the treatment holiday or control groups **who have an anti-belimumab antibody response at the 16-week follow-up visit (or the last immunogenicity assessment if the 16-week follow-up is not available).**

To:

Subjects in the treatment holiday and control groups who meet the protocol-defined withdrawal criteria specified in Section 4.4 at any time during Year 1 or the additional years will undergo assessments scheduled at the Exit visit (Week 52) in Table 2 except for dosing with belimumab. At approximately 16 weeks after the withdrawal visit or the last dose of belimumab as appropriate, these subjects will also undergo the assessments scheduled at the 16-week follow-up visit; the 6 month follow-up visit is scheduled only for these discontinued subjects in the treatment holiday or control groups.

Rationale: Provides clarification of protocol wording. The sentence should have been truncated prior to protocol amendment 5 publishing.

Change 12: Section 6.1.4 Definitions of SLE Flares Used in This Study

Change from:

- ~~2. A reproducible increase in serum creatinine of >20% or at least 0.3 mg/dL, accompanied by proteinuria (>1 g/24 hour equivalent), haematuria (≥ 4 red blood cells [RBCs]/high power field [hpf]), and/or RBC casts.~~
- ~~3. Treatment emergent, reproducible haematuria (≥ 11 to 20 RBCs/ hpf) or a reproducible increase in haematuria by 2 grades compared with baseline, associated with >25% dysmorphic RBCs, glomerular in origin, exclusive of menses, accompanied by either an~~

0.8 g increase in 24-hour urinary protein levels (equivalent) or new RBC casts [Alarcón-Segovia, 2003].

To:

2. A reproducible increase in **GFR** of >20% accompanied by **at least one of the following**: proteinuria (>1 g/24 hour equivalent), **and/or cellular (RBC or WBC)** casts [Alarcón-Segovia, 2003].

Rationale: Remove hematuria criteria from definition of renal flare.

Change 13: Section 8 Data Analysis and Statistical Considerations

Change from:

A total of approximately 135 subjects (50 in the treatment holiday group, 50 in the control group, and 35 in the long term discontinuation group) will be enrolled in this study.

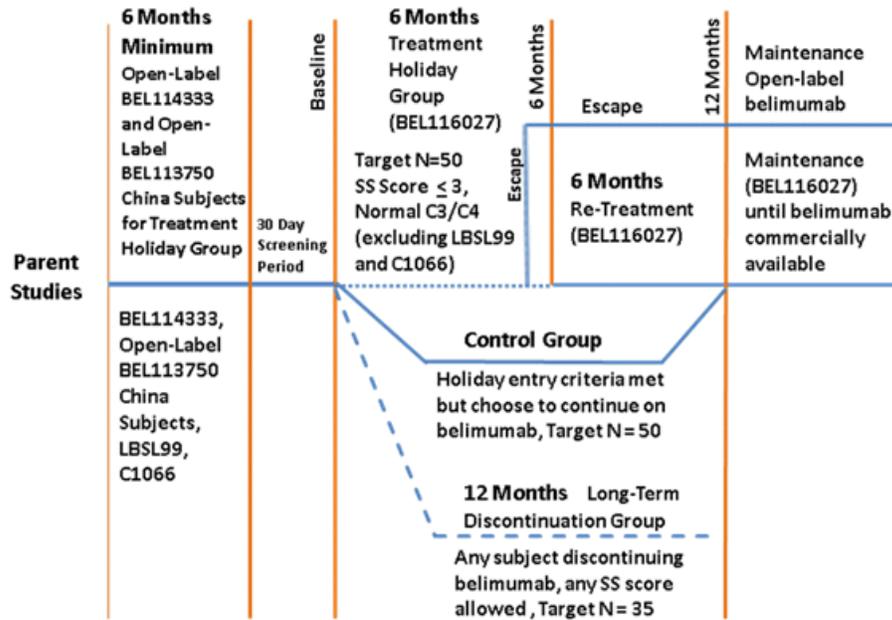
To:

Originally a total of approximately 135 subjects (50 in the treatment holiday group, 50 in the control group, and 35 in the long term discontinuation group) **were planned to be** enrolled in this study. **After 36 months had elapsed since study start, a reduction in sample size was agreed to with regulatory authorities, and a total of at least 71 subjects (at least 10 in the treatment holiday group, at least 26 in the control group, and 35 in the long term discontinuation group) will be the target sample size to be enrolled in this study.**

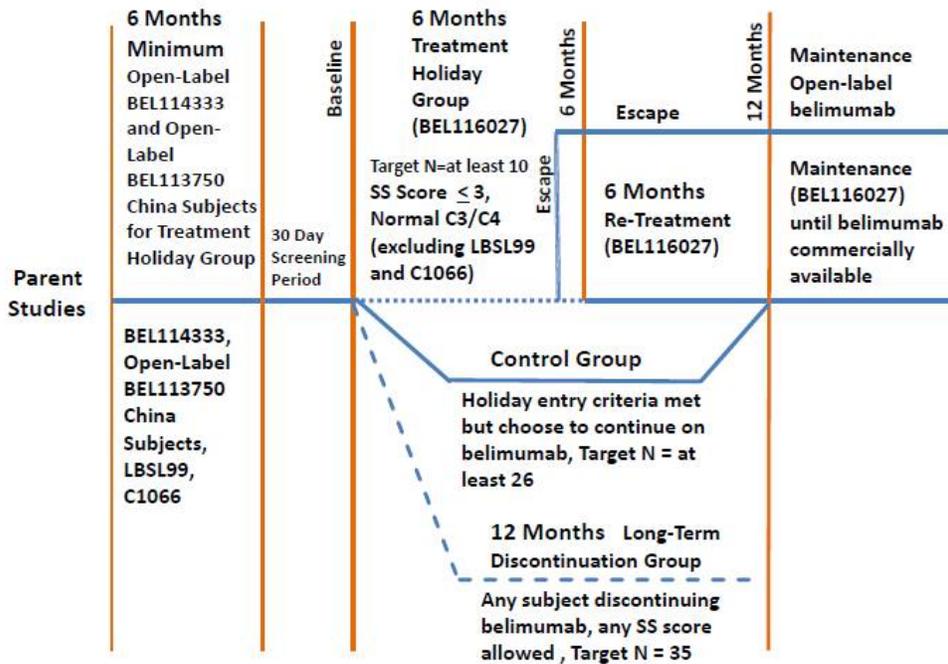
Rationale: Updated text for changes in target sample size as agreed upon with the EMA.

Change 14: Appendix 7, Amendment 01, Section 3.1, Figure 1

Change from:



To:



Rationale: Updated figure for changes in target sample size as agreed upon with the EMA.

Change 15: Appendix 7, Amendment 01, Section 3.1, Investigational Plan, Study Design***Change from:***

- **Treatment Holiday group:** The target enrolment for this group is 50 subjects.
- **Treatment Control group:** The target enrolment for this group is 50 subjects.

To:

- **Treatment Holiday group:** The target enrolment for this group is **at least 10** subjects.
- **Treatment Control group:** The target enrolment for this group is **at least 26** subjects.

Rationale: Updated text for changes in target sample size as agreed upon with the EMA.

Change 16: Appendix 7, Amendment 01, Section 3.1, Investigational Plan, Study Design***Change from:***

A 16-week follow-up visit will be scheduled for subjects in the treatment holiday and control groups **who withdraw prior to Week 52**. Additionally, a 6 month follow-up visit is required for those subjects in the treatment holiday or control groups **who have an anti-belimumab antibody response at the 16-week follow-up visit (or at the last immunogenicity assessment if 16-week follow-up is not available)**.

To:

A 16-week follow-up visit will be scheduled for subjects in the treatment holiday and control groups **after the withdrawal visit or the last dose of belimumab as appropriate**. Additionally, a 6 month follow-up visit is required for those subjects in the treatment holiday or control groups.

Rationale: Provides clarification of protocol wording. The sentence regarding 6-month follow-up should have been truncated prior to protocol amendment 5 publishing.

Change 17: Appendix 7, Amendment 01, Section 3.2, Discussion of Design***Change from:***

The target sample size of 50 subjects in each of the treatment holiday and control groups is based on estimates of subject eligibility and number of subjects from continuation study BEL114333 and China subjects in BEL113750 receiving open-label belimumab for at least 6 months, is anticipated to provide consent to participate in this study.

To:

The target sample size of **at least 10** subjects in the treatment holiday **group** and **at least 26 subjects in the control group** is based on estimates of subject eligibility and number of subjects from continuation study BEL114333 and China subjects in BEL113750 receiving open-label belimumab for at least 6 months, is anticipated to provide consent to participate in this study.

Rationale: Updated text for changes in target sample size as agreed upon with the EMA.

Protocol Amendment 05

Protocol amendment 05 applies to all countries and sites

Description of Changes

Changes are highlighted in bold.

Change 1: Study Assessments and Procedures, Table 2, Time and Events Table (Year 1), footnote 6.**Change from:**

6. Complete assessment prior to belimumab dosing for subjects in the control group (to Week 48) and for subjects in the treatment holiday group (during Weeks 24 to 48 or earlier in the event of a flare).

To:

6. Complete assessment prior to belimumab dosing for subjects in the control group (to Week 48) and for subjects in the treatment holiday group (during Weeks 24 to 48 or earlier in the event of a flare). **Immunogenicity testing includes quantifying the amount of belimumab present in the samples using the belimumab PK assay.**

Rationale: Clarifies PK analysis is needed for analysis of confirmed ADA positive samples.

Change 2: Time Period and Frequency of Detecting AEs and SAEs

This change affects Section 6.4.7 Time Period and Frequency of Detecting AEs and SAEs, last paragraph

Change from:

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated

procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.4.10.

To:

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.4.10. **Note: for China sites, serious AEs should be recorded from the time the consent form is signed until the 16-week follow up contact for subjects in the treatment holiday and control groups, or until the Week 52 visit for subjects in the long-term discontinuation group. GSK's pharmacovigilance safety database will contain all SAEs occurring after the first dose of investigational product plus any SAEs related to study participation occurring after the subject signs the informed consent form. SAEs that occur after signing the informed consent form but before the first dose of investigational product that are not considered to be related to study participation will not be entered into the GSK pharmacovigilance safety database, and will be summarized separately in the clinical study report.**

Rationale: This change clarifies China sites are able to record all SAEs from when the subject signs the informed consent form, not just reporting SAEs related to study participation or a GSK concomitant medication.

Change 3: Immunogenicity

This change affects Section 6.4.16 Immunogenicity, first paragraph.

Change from:

Serum samples will be collected for immunogenicity assessment. All samples should be collected prior to dosing (where appropriate) as specified in the appropriate Time and Events schedule (Table 2 or Table 3). Note that serum samples for immunogenicity must be collected pre-dose at the time of dosing from subjects in the treatment holiday group who experience a severe flare prior to Week 24 and consequently receive open-label belimumab as rescue. For non-dosing visits, assessment can be performed at any time during the visit.

To:

Serum samples will be collected for immunogenicity assessment. All samples should be collected prior to dosing (where appropriate) as specified in the appropriate Time and Events schedule (Table 2 or Table 3). Note that serum samples for immunogenicity must

be collected pre-dose at the time of dosing from subjects in the treatment holiday group who experience a severe flare prior to Week 24 and consequently receive open-label belimumab as rescue. For non-dosing visits, assessment can be performed at any time during the visit. **An attempt will be made to determine the amount of belimumab (PK) present in immunogenicity samples with confirmed anti-drug binding antibodies (ADA). The belimumab level in these samples will be used in the interpretation of ADA results and will be included in the immunogenicity section in the CSR.**

Rationale: Clarifies PK analysis is needed for analysis of confirmed ADA positive samples.

Change 4: Immunogenicity

This change affects Section 6.4.16 Immunogenicity, 3rd and 4th paragraphs.

Change from:

All immunogenicity testing will be carried out according to the multi-tier assay testing scheme including the detection of anti-drug binding antibodies (ADA, including 3-steps of screening, confirmation/specificity and titration) and the detection of anti-drug neutralizing antibodies (Nab).

All samples will be tested in ADA screening step. Any samples tested positive in the screening step will then be tested using an ADA confirmation step. Any confirmed positive samples in the confirmation will be further tested in the titration to obtain ADA titer values and in the Nab assay to evaluate the presence of neutralizing antibodies. The incidence of subjects with confirmed positive ADA responses with titers and positive Nab will be reported, respectively at the end of the study.

To:

All immunogenicity testing will be carried out according to the multi-tier assay testing scheme including the detection of anti-drug binding antibodies (ADA, including 3-steps of screening, confirmation/specificity and titration) and the detection of anti-drug neutralizing antibodies (Nab). **Note: Nab testing will not be performed in China.**

All samples will be tested in ADA screening step. Any samples tested positive in the screening step will then be tested using an ADA confirmation step. Any confirmed positive samples in the confirmation will be further tested in the titration to obtain ADA titer values and in the Nab assay to evaluate the presence of neutralizing antibodies. The incidence of subjects with confirmed positive ADA responses with titers and positive Nab will be reported, respectively at the end of the study. **However, Nab results will not be available for China subjects.**

Rationale: Clarifies the immunogenicity testing process for China subjects, because the Nab test will not be performed in China.

Change 5: Pharmacokinetics

This change affects Section 6.6 Pharmacokinetics

Change from:

Collect blood samples for measurement of serum belimumab concentrations from subjects in the treatment holiday and control groups at selected sites at the times specified in the Time and Events Table (Table 2). Only one PK sampling for the treatment holiday group between Weeks 0 and 16 can be performed at any time during the visit. Otherwise, sampling must be performed prior to dosing (pre-dose sample) at Day 0 and Weeks 8 and 16. Sampling must be performed pre-dose and post-dose (at the end of the belimumab infusion) at Weeks 24 and 52 (or earlier if belimumab is re-started before Week 24 in the event of a severe flare by using the escape option). For non-dosing visits, assessment can be performed once at any time during the subject's visit. Subjects in the long-term discontinuation group will have one PK sampling performed at any time during the visit between Weeks 0 and 24. PK sampling for the long-term discontinuation group is not performed after Week 24. Long-term discontinuation subjects withdrawing before Week 24 will have one PK sampling performed at any time during the EXIT visit. PK sampling for long-term discontinuation subjects withdrawing after Week 24 is not performed at the EXIT visit. Samples will be analysed at a central laboratory.

To:

Collect blood samples for measurement of serum belimumab concentrations from subjects in the treatment holiday and control groups at selected sites at the times specified in the Time and Events Table (Table 2). Only one PK sampling for the treatment holiday group between Weeks 0 and 16 can be performed at any time during the visit. Otherwise, sampling must be performed prior to dosing (pre-dose sample) at Day 0 and Weeks 8 and 16. Sampling must be performed pre-dose and post-dose (at the end of the belimumab infusion) at Weeks 24 and 52 (or earlier if belimumab is re-started before Week 24 in the event of a severe flare by using the escape option). For non-dosing visits, assessment can be performed once at any time during the subject's visit. Subjects in the long-term discontinuation group will have one PK sampling performed at any time during the visit between Weeks 0 and 24. PK sampling for the long-term discontinuation group is not performed after Week 24. Long-term discontinuation subjects withdrawing before Week 24 will have one PK sampling performed at any time during the EXIT visit. PK sampling for long-term discontinuation subjects withdrawing after Week 24 is not performed at the EXIT visit. Samples will be analysed at a central laboratory. **PK assessment will also be used to determine belimumab concentration in confirmed positive immunogenicity samples.**

Rationale: Clarifies PK analysis is needed for analysis of confirmed ADA positive samples.

Change 6: Appendix 5: Clinical Laboratory Tests

This change affects Section 11.5, Appendix 5: Clinical Laboratory Tests, Liver event follow-up assessments category.

Add:**IgG, hepatitis delta antibody, fractionated bilirubin, and serum acetaminophen**

Rationale: Addition of laboratory tests mentioned in Section 6.4.1 Liver chemistry stopping and follow up criteria. Note: ANA is already shown under the Autoantibodies sub-heading, hep B viral DNA is already shown under the Modified Chem-20/Other sub-heading, and the eosinophils are already shown under the Hematology sub-heading.

Protocol Amendment 04

Protocol amendment 04 applies to all countries and sites

Description of Changes

Changes are highlighted in bold.

Change 1: SPONSOR INFORMATION PAGE

This change affects the SPONSOR INFORMATION PAGE, Sponsor Medical Monitors Contact Information and Case Management Group sections.

Change from:

Sponsor Medical Monitor Contact Information:

Primary Medical Monitor

PPD [REDACTED] DO (Director, Immuno-Inflammation Medicine Development Center)

Tel: PPD [REDACTED]

Mobile: PPD [REDACTED]

Backup Medical Monitor

PPD [REDACTED] DO (Director, Immuno-Inflammation Medicine Development Center)

Tel: PPD [REDACTED]

Mobile: PPD [REDACTED]

Sponsor Serious Adverse Events (SAE) Contact Information:

Case Management Group, Global Clinical Safety and Pharmacovigilance (GCSP)

Email: PPD

Fax: PPD

To:

Sponsor Medical Monitor Contact Information:

Primary Medical Monitor

PPD DO (Director, Immuno-Inflammation Medicine Development Center)

Tel: PPD

Mobile: PPD

Backup Medical Monitor

PPD DO (Director, Immuno-Inflammation Medicine Development Center)

Tel: PPD

Mobile: PPD

Sponsor Serious Adverse Events (SAE) Contact Information:

Case Management Group, Global Clinical Safety and Pharmacovigilance (GCSP)

Email: PPD

Fax: PPD

Regulatory Agency Identifying Number(s): 9970

Rationale: Update telephone numbers for the Primary and Backup Medical Monitors, and the Case Management Group email address and fax number. The Regulatory Agency Identifying Number has been added because United States clinical study sites have joined this clinical trial.

Change 2: Study Design

This change affects Section 3.1, Study Design, 3rd paragraph.

Change from:

The study consists of a screening phase of up to 30 days, a 52-week treatment/observation phase with an escape option, a maintenance phase, and a follow-up phase. The screening phase will allow an assessment of the SELENA SLEDAI score and complement (C3 and C4) levels as part of the eligibility criteria for subjects in the treatment holiday and control groups. All subjects will attend clinic visits for efficacy and safety assessments every 4 weeks for 52 weeks. At the end of the 52 week period, subjects in the treatment holiday and control groups will have the option to continue belimumab therapy in the maintenance phase of this study only if belimumab is not commercially available in a subject's country of participation. This maintenance phase

will last until such time as belimumab becomes commercially available in a subject's country of participation, or the Sponsor decides to terminate **further development of belimumab for SLE.**

To:

The study consists of a screening phase of up to 30 days, a 52-week treatment/observation phase with an escape option, a maintenance phase, and a follow-up phase. The screening phase will allow an assessment of the SELENA SLEDAI score and complement (C3 and C4) levels as part of the eligibility criteria for subjects in the treatment holiday and control groups. All subjects will attend clinic visits for efficacy and safety assessments every 4 weeks for 52 weeks. At the end of the 52 week period, subjects in the treatment holiday and control groups will have the option to continue belimumab therapy in the maintenance phase of this study only if belimumab is not commercially available in a subject's country of participation. This maintenance phase will last until such time as belimumab becomes commercially available in a subject's country of participation, **or the Sponsor discontinues the maintenance phase of the study for China subjects with the provision for China subjects to elect to participate in a different protocol to continue to receive belimumab,** or the Sponsor decides to terminate **the study. Safety reporting will be as specified in the protocol the subject participates in.**

Rationale: This change allows the sponsor the option to discontinue the maintenance phase of the study for China subjects. This change also allows the sponsor the option of terminating the study while still continuing the development/marketing of belimumab for SLE. Provision of intravenous belimumab to China study subjects who participated in the maintenance phase this trial may be offered through a separate continuation protocol, such as the 200140 protocol, which was submitted to the China FDA in October 2014 and approval is anticipated by July 2017. If the 200140 protocol is approved, then participation is voluntary. Japanese subjects who enter the maintenance phase of the BEL116027 study will be allowed to continue the maintenance phase because the Japanese regulatory framework does not include expanded access or compassionate use programs. Belimumab has been available in Korea since the first quarter of 2015.

Change 3: Treatment after the End of the Study

This change affects Section 5.6 Treatment after the End of the Study, first paragraph.

Change from:

Eligible subjects in the treatment holiday and control groups may continue to receive belimumab therapy every 4 weeks under the maintenance phase of this protocol until the subject withdraws from the study, or the subject elects to participate in another belimumab continuation study for SLE, or belimumab becomes commercially available in a subject's country of participation, or upon the decision by the sponsor to discontinue **development/marketing of belimumab for SLE.** Subjects in the treatment holiday and control groups who complete Week 52 of this study are not eligible to receive further

treatment with belimumab in the maintenance phase of this study if belimumab is commercially available in the subject's country of participation.

To:

Eligible subjects in the treatment holiday and control groups may continue to receive belimumab therapy every 4 weeks under the maintenance phase of this protocol until the subject withdraws from the study, or the subject elects to participate in another belimumab continuation study for SLE, **or the Sponsor discontinues the maintenance phase of the study for China subjects with the provision for China subjects to elect to participate in a different protocol to continue to receive belimumab**, or belimumab becomes commercially available in a subject's country of participation, or upon the decision by the sponsor to discontinue **the study. Safety reporting will be as specified in the protocol the subject participates in.** Subjects in the treatment holiday and control groups who complete Week 52 of this study are not eligible to receive further treatment with belimumab in the maintenance phase of this study if belimumab is commercially available in the subject's country of participation.

Rationale: This change allows the sponsor the option to discontinue the maintenance phase of the study for China subjects. This change also allows the sponsor the option of terminating the study while still continuing the development/marketing of belimumab for SLE. Provision of intravenous belimumab to China study subjects who participated in the maintenance phase this trial may be offered through a separate continuation protocol, such as the 200140 protocol, which was submitted to the China FDA in October 2014 and approval is anticipated by July 2017. If the 200140 protocol is approved, then participation is voluntary. Japanese subjects who enter the maintenance phase of the BEL116027 study will be allowed to continue the maintenance phase because the Japanese regulatory framework does not include expanded access or compassionate use programs. Belimumab has been available in Korea since the first quarter of 2015.

Change 4: Time and Events Table (Year 1)

This change affects Section 6, Study Assessments and Procedures, Table 2, Time and Events Table (Year 1), footnote 3.

Change from:

3. The 16 week follow-up visit will occur at approximately 16 weeks after last dose of investigational product for subjects in the control group who withdraw at any time during the study **but do not wish to enter the long-term discontinuation group and be followed for a further 12 months** or for subjects in the treatment holiday group who withdraw from the study from Week 24 onwards (Visit 7) during the belimumab re-introduction period. The 16-week and 6 month follow-up visits do not apply to subjects in the long-term discontinuation group.

To:

3. The 16 week follow-up visit will occur at approximately 16 weeks after last dose of investigational product for subjects in the control group who withdraw at any time during the study, or for subjects in the treatment holiday group who withdraw from the study from Week 24 onwards (Visit 7) during the belimumab re-introduction period. The 16-week and 6 month follow-up visits do not apply to subjects in the long-term discontinuation group.

Rationale: Correction of the typographical error by removing the wording as no switching between the three groups is allowed. This wording should not have appeared in the footnote.

Change 5: Liver chemistry stopping and follow up criteria.

This change affects Section 6.4.1. Updates to the entire section below are in **bold**. Removed text has been shown by strikethroughs.

Updated Section:

6.4.1 Liver chemistry stopping and follow up criteria

Phase III-IV liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance) [James, 2009; **Le Gal, 2005**]. For subjects in the treatment holiday group having belimumab therapy re-introduced from Week 24 onwards or escaping to the maintenance phase of the study prior to Week 24, subjects in the control group, or any subject entering the maintenance phase of the study, the following applies:

Phase III-IV liver chemistry stopping criteria 1-5 are defined below and in Appendix 3:

1. ALT \geq 3xULN and bilirubin \geq 2xULN (>35% direct bilirubin) (or ALT \geq 3xULN and INR>1.5, if INR measured)

NOTE: if serum bilirubin fractionation is not immediately available, withdraw belimumab for that subject if ALT \geq 3xULN and bilirubin \geq 2xULN. Serum bilirubin fractionation should be 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.

2. ALT \geq 8xULN.

3. ALT \geq 5xULN but <8 xULN persists for \geq 2 weeks **OR** ALT \geq 3xULN but <5 xULN **persists for \geq 4 weeks**

4. ALT \geq 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

5. ALT \geq 5xULN but <8 xULN and cannot be monitored weekly for \geq 2 weeks **OR** ALT \geq 3xULN but <5 xULN and cannot be monitored weekly for \geq 4 weeks

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- Immediately ~~withdraw~~ **discontinue** belimumab for that subject
- Report the event to GSK within 24 hours ~~of learning its occurrence~~
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT \geq 3xULN and bilirubin \geq 2xULN (>35% direct) (or ALT \geq 3xULN and INR>1.5, if INR measured); INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed ‘Hy’s Law’, must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

NOTE: if serum bilirubin fractionation is not immediately available, withdraw belimumab for that subject if ALT \geq 3xULN and bilirubin \geq 2xULN. Serum bilirubin fractionation should be 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.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- ~~Withdraw the subject from the study after completion of the liver chemistry monitoring.~~
- ~~Do not re-challenge with belimumab.~~ Do not restart subject with belimumab unless GSK Medical Governance approval is granted (refer to Section 6.4.1.1)

Monitoring for liver chemistry stopping criterion 1:

- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values

Monitoring for liver chemistry stopping criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic within 24-72 hrs for repeat liver chemistries and liver event follow up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Phase III-IV Liver Chemistry Increased Monitoring Criteria With Continued Therapy

Subjects with ALT \geq 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 ~~which exhibit a decrease to~~ ALT $\geq 3 \times \text{ULN}$, but $< 5 \times \text{ULN}$ and bilirubin $< 2 \times \text{ULN}$ without hepatitis symptoms or rash **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
- Can continue belimumab
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- **If ALT decreases from ALT $\geq 5 \times \text{ULN}$ and $< 8 \times \text{ULN}$ to $\geq 3 \times \text{ULN}$ but $< 5 \times \text{ULN}$, continue to monitor liver chemistries weekly.**
- If, after 4 weeks of monitoring, ALT $< 3 \times \text{ULN}$ and bilirubin $< 2 \times \text{ULN}$, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

Follow-up Assessments For Liver Stopping Criteria 1-5

Make every attempt to carry out the liver event follow up assessments described below:

- Viral hepatitis serology including:
 - 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
- **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. NOTE: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [LeGal, 2005].**
- Blood sample for PK analysis, obtained within approximately one to two weeks after the liver event. Record the date/time of the PK blood sample draw and the date/time of the last dose of belimumab prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Fractionate bilirubin, if total bilirubin $\geq 2xULN$.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

The following are required for subjects with ALT $\geq 3xULN$ and bilirubin $\geq 2xULN$ (>35% direct) **or ALT $\geq 3xULN$ and INR>1.5, if INR measured**; but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and 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.
- ~~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. NOTE: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) as outlined in: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793/>.~~
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

For long-term discontinuation group subjects found to have met the liver stopping criteria without receiving belimumab, investigators will apply the withdrawal criteria in Section 4.4.

Rationale: Include updates to this section.

Change 6: Study Treatment Restart

This change affects Section 6.4.1.1.

Add new section:

6.4.1.1 Study Treatment Restart

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 is signed by the subject

If GSK Medical Governance approval to restart 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 drug induced liver injury [DILI]) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, 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 6.4.8.

Rationale: Add new section for restarting investigational product after a subject has experienced a liver event.

Change 7: Interim Analysis

This change affects Section 8.1.6 Interim Analysis

Change from:

An **unblinded** interim analysis of the data in this **continuation** trial may be performed to support a submission to regulatory authorities relating to marketing authorization (e.g., to summarize and submit this long term safety data to regulatory authorities in the initial BLA and other marketing authorization submissions). Additional interim analyses may be required to support subsequent safety updates to regulatory authorities.

To:

An interim analysis of the data in this trial may be performed to support a submission to regulatory authorities relating to marketing authorization (e.g., to summarize and submit this long term safety data to regulatory authorities in the initial BLA and other marketing authorization submissions). Additional interim analyses may be required to support subsequent safety updates to regulatory authorities.

Rationale: Two of the three subjects groups in this study will receive open-label belimumab, and removal of the typographical error of “unblinded” in the sentence is appropriate. Additionally, this study is not a “continuation” trial as the primary and secondary objectives state specific objectives, and removing “continuation” corrects this typographical error.

Change 8: Study and Site Closure

This change affects Section 9.5 Study and Site Closure, first paragraph.

Change from:

Subjects recruited into this study will continue to receive treatment with belimumab until such time as belimumab becomes commercially available in Northeast Asia, or the subject elects to participate in another belimumab continuation study for SLE, or until either the subject's physician withdraws the subject from the study or upon the decision by the sponsor to discontinue **further development of belimumab for SLE**. Upon completion of treatment, every effort should be made to evaluate subjects for Week 16 post-treatment follow-up visit and the 6-month post-treatment visit. Once all reasonable efforts have been made, the study will be considered complete/terminated.

To:

Subjects recruited into this study will continue to receive treatment with belimumab until such time as belimumab becomes commercially available in Northeast Asia, or the subject elects to participate in another belimumab continuation study for SLE, **or the Sponsor discontinues the maintenance phase of the study for China subjects with the provision for China subjects to elect to participate in a different protocol to**

continue to receive belimumab, or until either the subject's physician withdraws the subject from the study, or upon the decision by the sponsor to discontinue **the study**. **Safety reporting will be as specified in the protocol the subject participates in.** Upon completion of treatment, every effort should be made to evaluate subjects for Week 16 post-treatment follow-up visit and the 6-month post-treatment visit. Once all reasonable efforts have been made, the study will be considered complete/terminated.

Rationale: This change allows the sponsor the option to discontinue the maintenance phase of the study for China subjects. This change also allows the sponsor the option of terminating the study while still continuing the development/marketing of belimumab for SLE. Provision of intravenous belimumab to China study subjects who participated in the maintenance phase this trial may be offered through a separate continuation protocol, such as the 200140 protocol, which was submitted to the China FDA in October 2014 and approval is anticipated by July 2017. If the 200140 protocol is approved, then participation is voluntary. Japanese subjects who enter the maintenance phase of the BEL116027 study will be allowed to continue the maintenance phase because the Japanese regulatory framework does not include expanded access or compassionate use programs. Belimumab has been available in Korea since the first quarter of 2015.

Change 9: References

This change affects Section 10, References.

Add:

Le Gal F, Gordien E, Affolabi D, et al. 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):2363–9.

Rationale: Now referenced in updated Section 6.4.1 Liver chemistry stopping and follow up criteria.

Change 10: Appendix 7: Country Specific Requirements

This change affects Section 11.7, Appendix 7: Country Specific Requirements, Amendment 01, Section 3.1 Investigational Plan, Study Design, 3rd paragraph.

Change from:

The study consists of a screening phase of up to 30 days, a 52-week treatment/observation phase with an escape option, a maintenance phase, and a follow-up phase. The screening phase will allow an assessment of the SELENA SLEDAI score and complement (C3 and C4) levels as part of the eligibility criteria for subjects in the treatment holiday and control groups. All subjects will attend clinic visits for efficacy and safety assessments every 4 weeks for 52 weeks. At the end of the 52 week period, subjects in the treatment holiday and control groups will have the option to continue

belimumab therapy in the maintenance phase of this study only if belimumab is not commercially available in a subject's country of participation. This maintenance phase will last until such time as belimumab becomes commercially available in a subject's country of participation, or the Sponsor decides to terminate **further development of belimumab for SLE.**

To:

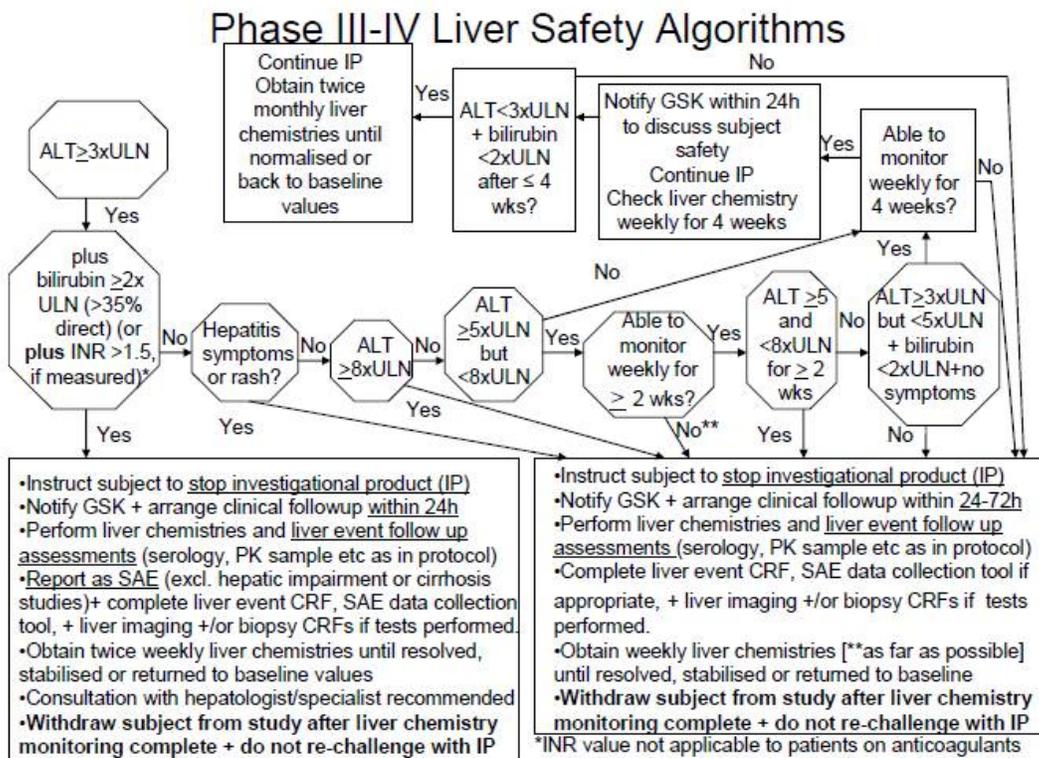
The study consists of a screening phase of up to 30 days, a 52-week treatment/observation phase with an escape option, a maintenance phase, and a follow-up phase. The screening phase will allow an assessment of the SELENA SLEDAI score and complement (C3 and C4) levels as part of the eligibility criteria for subjects in the treatment holiday and control groups. All subjects will attend clinic visits for efficacy and safety assessments every 4 weeks for 52 weeks. At the end of the 52 week period, subjects in the treatment holiday and control groups will have the option to continue belimumab therapy in the maintenance phase of this study only if belimumab is not commercially available in a subject's country of participation. This maintenance phase will last until such time as belimumab becomes commercially available in a subject's country of participation, **or the Sponsor discontinues the maintenance phase of the study for China Subjects with the provision for China subjects to elect to participate in a different protocol to continue to receive belimumab,** or the Sponsor decides to terminate the study. **Safety reporting will be as specified in the protocol the subject participates in.**

Rationale: This change allows the sponsor the option to discontinue the maintenance phase of the study for China subjects. This change also allows the sponsor the option of terminating the study while still continuing the development/marketing of belimumab for SLE. Provision of intravenous belimumab to China study subjects who participated in the maintenance phase this trial may be offered through a separate continuation protocol, such as the 200140 protocol, which was submitted to the China FDA in October 2014 and approval is anticipated by July 2017. If the 200140 protocol is approved, then participation is voluntary. Japanese subjects who enter the maintenance phase of the BEL116027 study will be allowed to continue the maintenance phase because the Japanese regulatory framework does not include expanded access or compassionate use programs. Belimumab has been available in Korea since the first quarter of 2015.

Change 11: Appendix 3: Liver Chemistry Stopping and Follow up Criteria

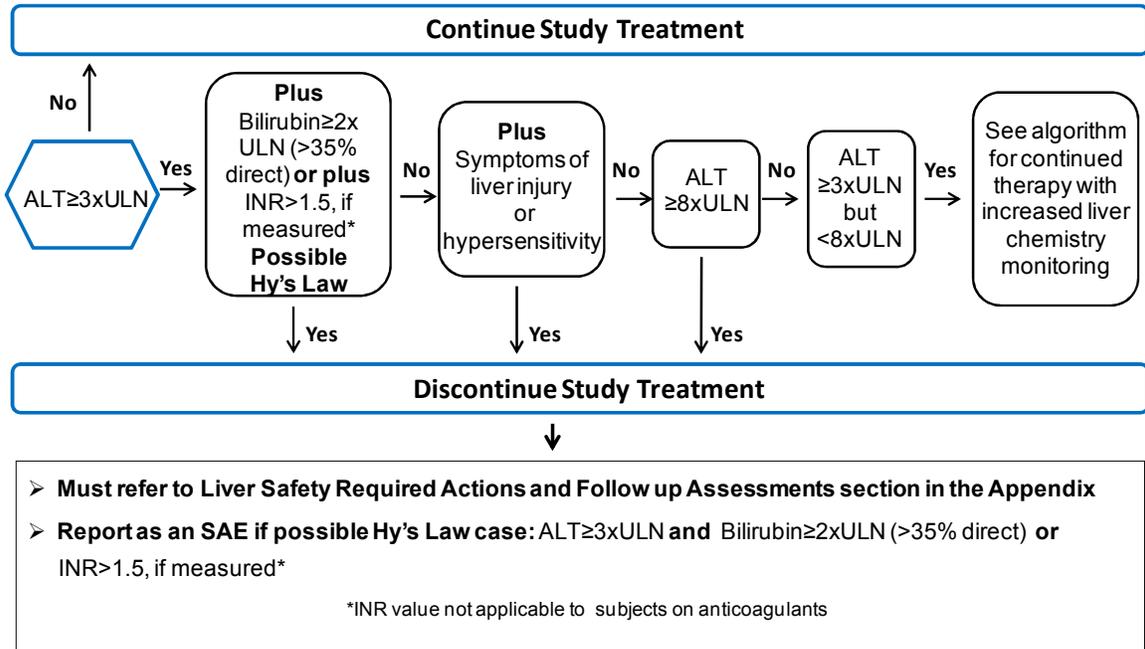
This change affects section 11.3; Appendix 3, Liver Chemistry Stopping and Follow up Criteria.

Change from:



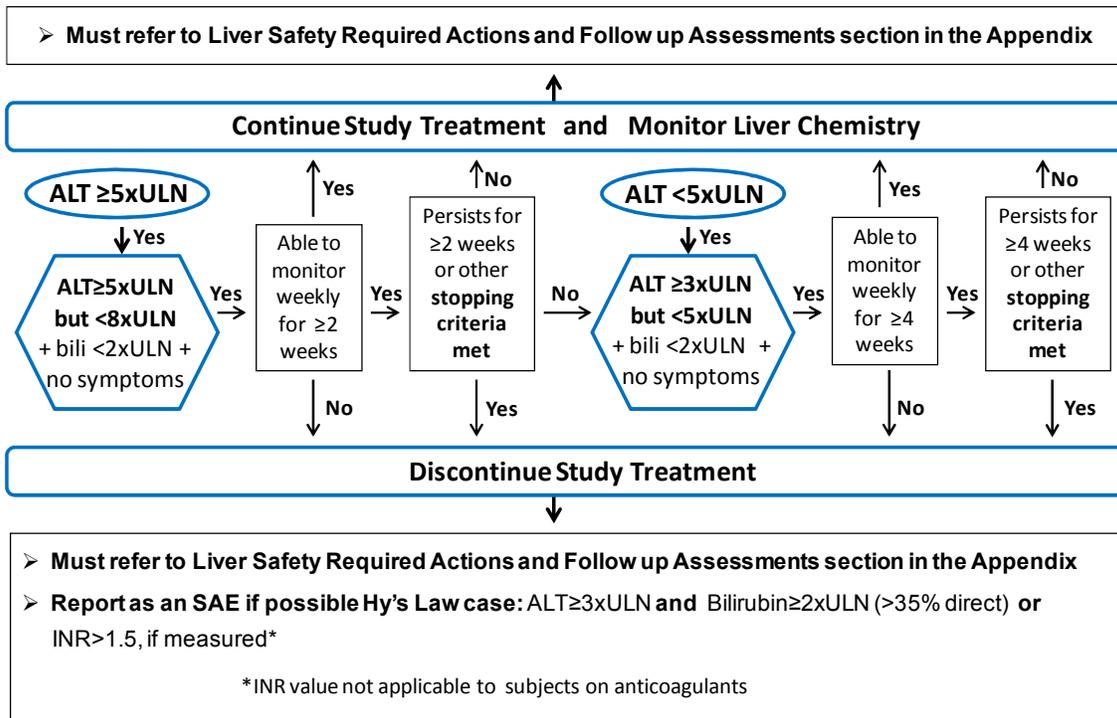
To:

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



- Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.4.1.

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 Section 6.4.1.

Rationale: Updated Phase III_IV Liver Safety Algorithm.

Protocol Amendment 03

Protocol amendment 03 applies to all countries and sites

Description of Changes

Changes are highlighted in bold.

Change 1: Sponsor Information Page

This change affects the Sponsor Information Page, Sponsor Serious Adverse Event (SAE) Contact Information:

Change from:

Email: PPD [REDACTED]

Fax: PPD [REDACTED]

To:

Email: PPD [REDACTED]

Fax: PPD [REDACTED]

Rationale: Update sponsor serious adverse event (SAE) contact information

Change 2: Investigational Product and Reference Therapy

This change affects Section 5.1, Study Treatments, Investigational Product and Reference Therapy, second paragraph, second sentence.

Change from:

At the start of the belimumab reintroduction period, subjects in the treatment holiday group will receive belimumab 10 mg/kg IV infused for 1 hour every 28 days.

To:

At the start of the belimumab reintroduction period, subjects in the treatment holiday group will receive belimumab 10 mg/kg IV infused for **over** 1 hour every 28 days.

Rationale: This corrects the typographical error as the word “over” was inadvertently omitted from the text.

Change 3: Investigational Product and Reference Therapy

This change affects Section 5.1, Study Treatments, Investigational Product and Reference Therapy, third paragraph, first sentence.

Change from:

Subjects in the control group will receive belimumab 10 mg/kg IV infused for 1 hour every 28 days from Day 0 onwards.

To:

Subjects in the control group will receive belimumab 10 mg/kg IV infused for **over** 1 hour every 28 days from Day 0 onwards.

Rationale: This corrects the typographical error as the word “over” was inadvertently omitted from the text.

Change 4: Treatment Assignment

This change affects Section 5.2 Treatment Assignment

Change from:

This is an open-label, non-randomized study. Site personnel will access **RAMOS NG**, the interactive voice response system (IVRS) to enrol the subject in the study and to log subject visits.

To:

This is an open-label, non-randomized study. Site personnel will access the interactive voice response system (IVRS) to enrol the subject in the study and to log subject visits. **Supplementary information is provided in the Study Procedures Manual (SPM).**

Rationale: A sponsor administrative change has prompted removing RAMOS NG as the designated interactive voice response system.

Change 5: Permitted Medications and Non-Drug Therapies

This change affects section 5.5.1 Permitted Medications and Non-Drug Therapies, Live vaccines.

Change from:

Note: Live vaccines are permitted **in this study and can be given at the investigator’s discretion.**

To:

Note: Live vaccines are permitted **for subjects in the long-term discontinuation group. Subjects in the control and treatment holiday groups are prohibited from receiving live vaccines.**

Rationale: This change clarifies that live vaccines can only be provided to subjects in the long-term discontinuation group, since these subjects will not be receiving belimumab during the study.

Change 6: Study Assessments and Procedures

This change affects Section 6, Time and Events Table (Year 1), Footnote 4 and corresponding “X” for Written Informed Consent at Visit 2.

Change from:

4 **For subjects in the control group only**, obtain written informed consent to participate in this study at the visit **prior to the last visit in the relevant SLE feeder continuation study.**

To:

4 Obtain written informed consent to participate in this study at the **Screening** visit.

Rationale: Because of the sponsor administrative change removing RAMOS NG as the IVRS system, this change clarifies that written informed consent will be obtained for all subjects at the screening visit.

Change 7: Critical Baseline Assessments

This change affects Section 6.2 Critical Baseline Assessments, second paragraph.

Change from:

The EXIT visit of the relevant SLE continuation protocol ((BEL114333, HGS1006-C1066, or LBSL99) from which the subject is recruited will serve as the Day 0 visit in this study. Subjects in the control group will be dosed with belimumab at the Day 0 visit as part of this protocol. These subjects must be able to receive the Day 0 dose in this study 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the previous open-label continuation study. Any procedures from this protocol or from the relevant previous open-label continuation protocols to be performed pre-dose must be completed before dosing subjects in the control group. **Subjects in the control group should sign the informed consent to participate in this study at the visit immediately prior to the EXIT visit to ensure a supply of belimumab for the Day 0 visit in this study. Subjects in the treatment holiday and long-term discontinuation groups**

should sign the informed consent at the screening visit and Day 0 visit, respectively of this study.

To:

The EXIT visit of the relevant SLE continuation protocol (BEL114333, HGS1006-C1066, or LBSL99) from which the subject is recruited will serve as the Day 0 visit in this study. Subjects in the control group will be dosed with belimumab at the Day 0 visit as part of this protocol. These subjects must be able to receive the Day 0 dose in this study 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the previous open-label continuation study. Any procedures from this protocol or from the relevant previous open-label continuation protocols to be performed pre-dose must be completed before dosing subjects in the control group. **Obtain written informed consent from all subjects to participate in this study at the Screening visit.**

Rationale: Because of the sponsor administrative change removing RAMOS NG as the IVRS system, this change clarifies that written informed consent will be obtained for all subjects at the screening visit.

Change 8: Study Assessments and Procedures

This change affects Section 6, Time and Events Table (Year 1), Footnote 12.

Change from:

12. Pharmacokinetic sampling at select sites for subjects in the control and treatment holiday groups; subjects in the treatment holiday group can have PK sampling performed at any time during the visit between Weeks 0 and 16. Otherwise, if on a dosing day, sampling must be performed prior to dosing. Collect blood samples pre-dose and post-dose at the end of the infusion at Weeks 24 and 52 (or earlier if belimumab is re-started before Week 24 in the event of a severe flare by using the escape option). Subjects in the long-term discontinuation group will have one PK sampling performed at any time during the visit between Weeks 0 and 24. PK sampling for the long-term discontinuation group is not performed after Week 24.

To:

12. Pharmacokinetic sampling at select sites for subjects in the control and treatment holiday groups; subjects in the treatment holiday group can have PK sampling performed at any time during the visit between Weeks 0 and 16. Otherwise, if on a dosing day, sampling must be performed prior to dosing. Collect blood samples pre-dose and post-dose at the end of the infusion at Weeks 24 and 52 (or earlier if belimumab is re-started before Week 24 in the event of a severe flare by using the escape option). Subjects in the long-term discontinuation group will have one PK sampling performed at any time during the visit between Weeks 0 and 24. PK sampling for the long-term discontinuation group is not performed after Week 24. **Long-term discontinuation subjects withdrawing before Week 24 will have one PK sampling performed at any time**

during the EXIT visit. PK sampling for long-term discontinuation subjects withdrawing after Week 24 is not performed at the EXIT visit.

Rationale: Clarifies PK sampling for long-term discontinuation subjects who withdraw from the study.

Change 9: Pharmacokinetics

This change affects Section 6.6, Pharmacokinetics

Change from:

Collect blood samples for measurement of serum belimumab concentrations from subjects in the treatment holiday and control groups at selected sites at the times specified in the Time and Events Table (Table 2). Only one PK sampling for the treatment holiday group between Weeks 0 and 16 can be performed at any time during the visit. Otherwise, sampling must be performed prior to dosing (pre-dose sample) at Day 0 and Weeks 8 and 16. Sampling must be performed pre-dose and post-dose (at the end of the belimumab infusion) at Weeks 24 and 52 (or earlier if belimumab is re-started before Week 24 in the event of a severe flare by using the escape option). For non-dosing visits, assessment can be performed once at any time during the subject's visit. Subjects in the long-term discontinuation group will have one PK sampling performed at any time during the visit between Weeks 0 and 24. PK sampling for the long-term discontinuation group is not performed after Week 24. Samples will be analysed at a central laboratory.

To:

Collect blood samples for measurement of serum belimumab concentrations from subjects in the treatment holiday and control groups at selected sites at the times specified in the Time and Events Table (Table 2). Only one PK sampling for the treatment holiday group between Weeks 0 and 16 can be performed at any time during the visit. Otherwise, sampling must be performed prior to dosing (pre-dose sample) at Day 0 and Weeks 8 and 16. Sampling must be performed pre-dose and post-dose (at the end of the belimumab infusion) at Weeks 24 and 52 (or earlier if belimumab is re-started before Week 24 in the event of a severe flare by using the escape option). For non-dosing visits, assessment can be performed once at any time during the subject's visit. Subjects in the long-term discontinuation group will have one PK sampling performed at any time during the visit between Weeks 0 and 24. PK sampling for the long-term discontinuation group is not performed after Week 24. **Long-term discontinuation subjects withdrawing before Week 24 will have one PK sampling performed at any time during the EXIT visit. PK sampling for long-term discontinuation subjects withdrawing after Week 24 is not performed at the EXIT visit.** Samples will be analysed at a central laboratory.

Rationale: Clarifies PK sampling for long-term discontinuation subjects who withdraw from the study.

Change 10: Regulatory and Ethical Considerations, Including the Informed Consent Process.

This change affects Section 9.2 Regulatory and Ethical Considerations, Including the Informed Consent Process, next to the last paragraph.

Change from:

Written informed consent must be obtained from each subject prior to participation in the study. **Subjects in the control group should sign the informed consent to participate in this study at the visit immediately prior to the EXIT visit to ensure a supply of belimumab for the Day 0 visit in this study. Subjects in the treatment holiday and long-term discontinuation groups should sign the informed consent at the Day 0 visit of this study.**

To:

Written informed consent must be obtained from each subject prior to participation in the study. **Obtain written informed consent from all subjects to participate in this study at the Screening visit.**

Rationale: Because of the sponsor administrative change removing RAMOS NG as the IVRS system, this change clarifies that written informed consent will be obtained for all subjects at the screening visit.

Protocol Amendment 02

Protocol amendment 02 is a global protocol amendment that applies to all involved countries and sites.

Description of Changes

Changes are highlighted in bold.

Change 1: Title page

This change affects the Title page, study title.

Change from:

A **Phase IV**, Open-label, Non-randomized, 52-Week Study to Evaluate Treatment Holidays and Rebound Phenomenon After Treatment With Belimumab 10 mg/kg in Systemic Lupus Erythematosus Subjects

To:

An Open-label, Non-randomized, 52-Week Study to Evaluate Treatment Holidays and Rebound Phenomenon After Treatment With Belimumab 10 mg/kg in Systemic Lupus Erythematosus Subjects

Rationale: Sponsor administrative change to remove reference to the study phase in the title, as study phases are interpreted differently in different participating countries, and thus removes any inconsistencies.

Change 2: Title page

This change affects the Title page.

Add:

Description: Protocol amendment number 02 is a global protocol amendment

Rationale: Clarifies that protocol amendment 02 is a global protocol amendment that applies to all involved countries and sites.

Change 3: Protocol Summary

This change affects the Protocol Summary Section, Study Design, first sentence.

Change from:

A phase **IV**, multi-centre, open-label, non-randomized, efficacy and safety study (including potential rebound) of:

To:

A phase **IIIB**, multi-centre, open-label, non-randomized, efficacy and safety study (including potential rebound) of:

Rationale: Sponsor administrative change of study phase reduces inconsistencies from some participating countries in which belimumab has not yet been approved.

Change 4: Study Design

This change affects Section 3.1 Study Design, first sentence.

Change from:

A phase **IV**, multi-centre, open-label, non-randomized, efficacy and safety study (including potential rebound) of:

To:

A phase **IIIB**, multi-centre, open-label, non-randomized, efficacy and safety study (including potential rebound) of:

Rationale: Sponsor administrative change of study phase reduces inconsistencies from some participating countries in which belimumab has not yet been approved.

Change 5: Progressive Multifocal Leukoencephalopathy

This change affects Section 6.4.13.1 Progressive Multifocal Leukoencephalopathy.

Change from:

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 judgement in further workup and clinical intervention as appropriate. Cases of suspected PML will be promptly reported to the sponsor.

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.

Rationale:

Updated wording addresses new information received by the Sponsor.

Change 6: Appendix 5

This change affects Appendix 5: Clinical Laboratory Tests.

Add:

aCL, ANA, BLyS protein, and Hepatitis B Viral DNA PCR Quantitative (HBV DNA)

Rationale: Corrects inadvertent omission in the Clinical Lab Test Appendix.

Protocol Amendment 01

Protocol amendment 01 for **China Specific** protocol Amendment **applies only to China and all China sites.**

Description of Changes

Changes are highlighted in bold.

Change 1: Title page

Add:

Description: Protocol amendment number 01 is a China specific protocol amendment

Rationale:

Clarifies Protocol Amendment 01 is China specific

Change 2: Protocol Summary, Study Design

This change affects Section Protocol Summary, study design, first paragraph, third sentence.

Change from:

All 3 subject groups will be recruited from the BEL114333 continuation study of belimumab in SLE.

To:

All 3 subject groups will be recruited from the BEL114333 continuation study of belimumab in SLE, **and from the open-label (OL) period BEL113750 for China subjects.**

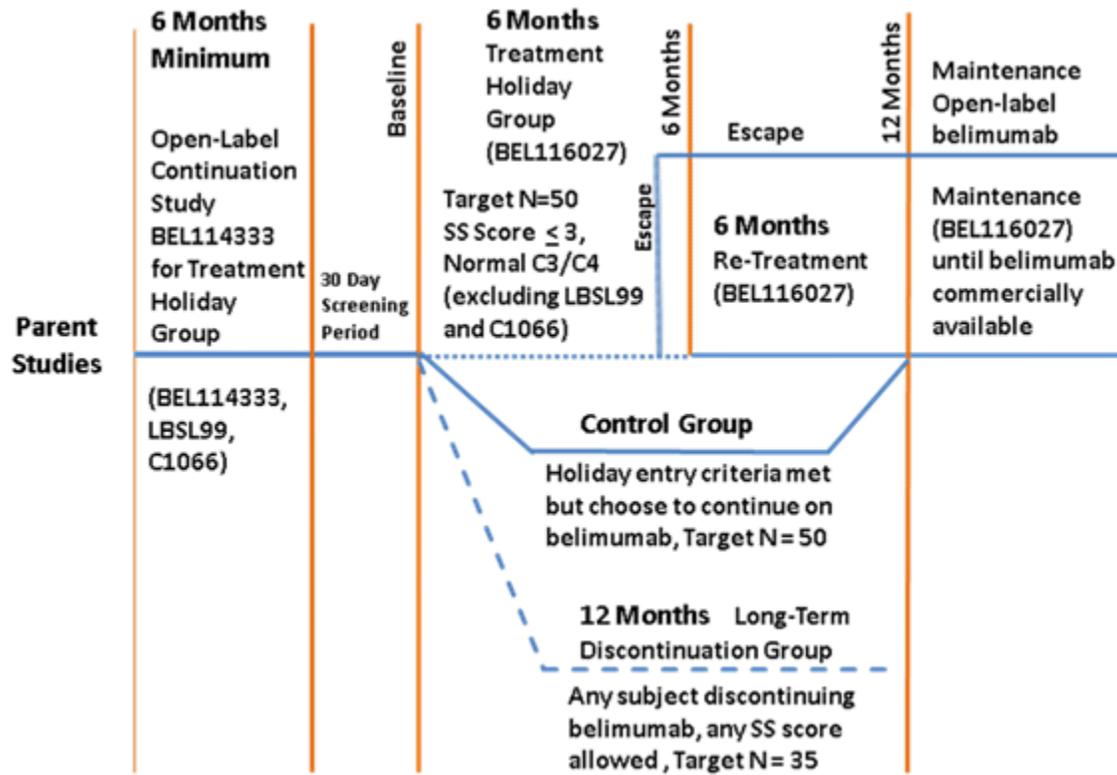
Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 3: Investigational Plan

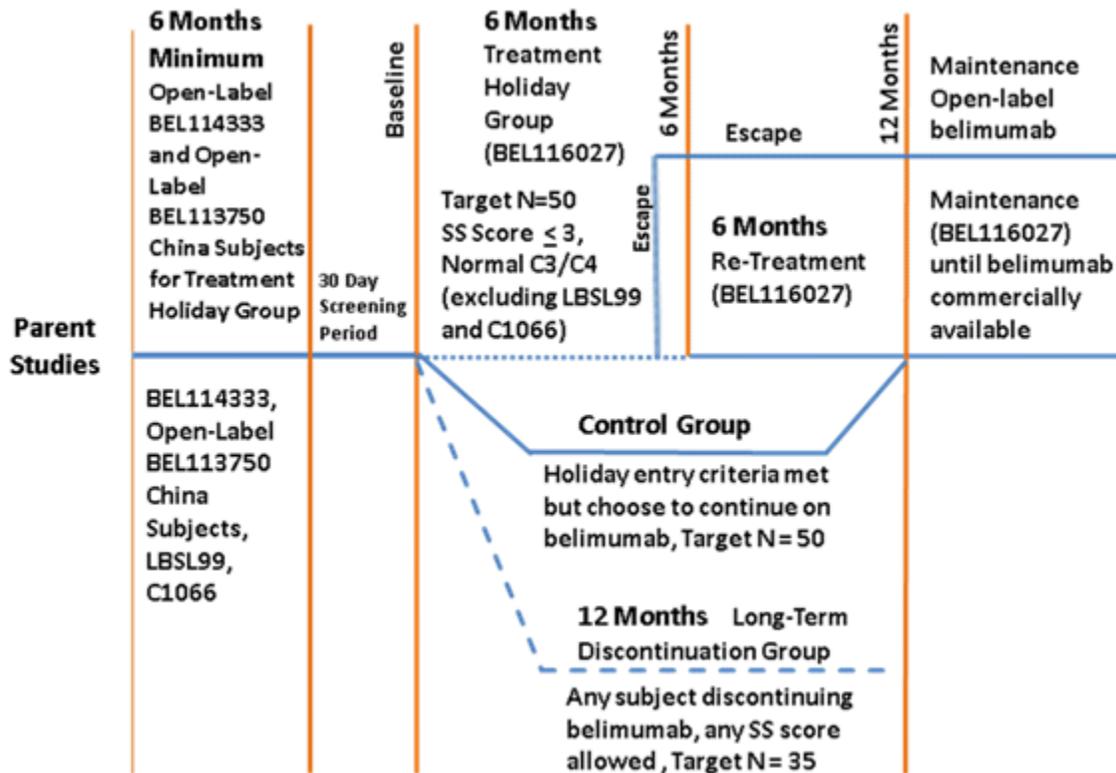
This change affects Section 3.1, Investigational Plan, Study Design, Figure 1, Study Schematic, 6 Months Minimum Column, and first descriptive sentence below schematic.

Change from:



Subjects will be recruited from 3 continuation studies of belimumab in SLE.

To:



Subjects will be recruited from 3 continuation studies of belimumab in SLE, **and from the open-label (OL) period of BEL113750 for China subjects.**

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 4: Investigational Plan

This change affects Section 3.1, Investigational Plan, Study Design, three different groups of subjects, bullet points.

Change from:

- Treatment Holiday group: This group will be used to assess the effect of temporary discontinuation (including rebound phenomenon) and re-introduction of belimumab 10 mg/kg therapy. These subjects will be recruited from the BEL114333 belimumab continuation study in subjects with SLE. Subjects will have been treated with belimumab for at least 6 months and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal. The target enrolment for this group is 50 subjects.

- Treatment Continuation control group: This group will serve as a control to the treatment holiday arm. These subjects will be recruited from the BEL114333 belimumab continuation study in subjects with SLE. Subjects will have been treated with belimumab for at least 6 months and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal but will continue their current treatment with belimumab 10 mg/kg. The target enrolment for this group is 50 subjects.
- Long-term Discontinuation group: This group will also be used to assess rebound phenomenon in SLE subjects who have discontinued therapy with belimumab 10 mg/kg and are expected to remain off belimumab therapy for at least 12 months but remain on standard of care therapy. These subjects will be recruited from 3 belimumab continuation studies in subjects with SLE (BEL114333; HGS1006-C1066; LBSL99). Subjects will have been treated with belimumab for at least 6 months in one of the continuation studies, but will have withdrawn from belimumab therapy for no longer than 8 weeks prior to entry into this study. These subjects may have any level of SLE disease activity. The target enrolment for this group is 35 subjects.

To:

- Treatment Holiday group: This group will be used to assess the effect of temporary discontinuation (including rebound phenomenon) and re-introduction of belimumab 10 mg/kg therapy. These subjects will be recruited from the BEL114333 belimumab continuation study in subjects with SLE, **and from the open-label period of BEL113750 for China subjects**. Subjects will have been treated with belimumab for at least 6 months and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal. The target enrolment for this group is 50 subjects.
- Treatment Continuation control group: This group will serve as a control to the treatment holiday arm. These subjects will be recruited from the BEL114333 belimumab continuation study in subjects with SLE, **and from the open-label period of BEL113750 for China subjects**. Subjects will have been treated with belimumab for at least 6 months and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal but will continue their current treatment with belimumab 10 mg/kg. The target enrolment for this group is 50 subjects.
- Long-term Discontinuation group: This group will also be used to assess rebound phenomenon in SLE subjects who have discontinued therapy with belimumab 10 mg/kg and are expected to remain off belimumab therapy for at least 12 months but remain on standard of care therapy. These subjects will be recruited from 3 belimumab continuation studies in subjects with SLE (BEL114333; HGS1006-C1066; LBSL99), **and from the open-label period of BEL113750 for China subjects**. Subjects will have been treated with belimumab for at least 6 months in one of the continuation studies, **and from the open-label period of BEL113750 for China subjects for at least 6 months**, but will have withdrawn from belimumab therapy for no longer than 8 weeks prior to entry into this study. These subjects may

have any level of SLE disease activity. The target enrolment for this group is 35 subjects.

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 5: Discussion of Design

This change affects Section 3.2 Discussion of Design.

Change from:

This study proposes to recruit subjects from ongoing open-label continuation studies of belimumab in SLE subjects in order to obtain an eligible population in the shortest timeframe. **There are 3 continuation studies of belimumab suitable for recruitment of subjects required for this study:**

- BEL114333: A Phase III open-label continuation of parent study BEL113750, which is an ongoing Phase III, double-blind, placebo-controlled study of belimumab in SLE subjects conducted in Japan, South Korea **and China**.
- HGS1006-C1066: An ongoing Phase III, open-label continuation study of parent study HGS1006-C1056 (BLISS 76), which enrolled and treated 268 SLE subjects with belimumab conducted in the United States
- LBSL99: An ongoing Phase II, open-label continuation study of parent study LBSL02, which enrolled and treated 296 SLE subjects with belimumab conducted in the United States and Canada.

Subjects eligible for inclusion in the treatment holiday group will have been treated with belimumab for at least 6 months in BEL114333, and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal.

Subjects eligible for inclusion in the control group will have been treated with belimumab for at least 6 months in BEL114333, and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal but elect to continue their current treatment with belimumab 10 mg/kg.

Subjects eligible for inclusion in the long-term discontinuation group may have any level of SLE disease activity; will have been treated with belimumab for at least 6 months in any of the 3 continuation studies mentioned above, and have discontinued belimumab therapy for no longer than 8 weeks prior to entry into this study and intend to remain off belimumab treatment for the 12 months of this study but to remain on standard of care therapy.

Subjects eligible for inclusion in the treatment holiday group will not be recruited from the long-term continuation studies LBSL99 or HGS1006-C1066, due to regulatory commitments for completing 10 years and 5 years on treatment, respectively. However, subjects who discontinue belimumab treatment in studies LBSL99 or HGS1006-C1066 can be recruited into the long-term discontinuation group in the present study.

For subjects entering the study, a minimum of 6 months previous participation in an open-label continuation studies will provide subjects initially randomized to placebo in parent studies with the opportunity to reach sufficient biological activity to achieve a belimumab pharmacological and/or clinical response.

The target sample size of 50 subjects in each of the treatment holiday and control groups is based on estimates of subject eligibility and number of subjects from continuation study BEL114333, is anticipated to provide consent to participate in this study. The target sample size of 35 subjects for the long-term discontinuation group is based on practical considerations of numbers of subjects anticipated to drop-out and not on statistical considerations.

Enrolment of subjects from the 3 belimumab continuation into the long-term discontinuation group will remain open while recruitment to the treatment holiday and control groups is ongoing or until 36 months have elapsed since study start. A target sample size of 35 subjects in the long-term discontinuation group is anticipated.

Because this study is non-randomized, subjects and investigators from study BEL114333 will jointly decide upon which of the three groups to enrol into. Subjects recruited from the HGS1006-C1066 and the LBSL99 studies may only choose to enter the long-term discontinuation group, as they elect to no longer receive further belimumab therapy.

To:

This study proposes to recruit subjects from **3** ongoing open-label continuation studies of belimumab in SLE subjects **as well as from the open-label period of BEL113750 for China subjects** in order to obtain an eligible population in the shortest timeframe:

- BEL114333: A Phase III open-label continuation of parent study BEL113750, which is an ongoing Phase III, double-blind, placebo-controlled study of belimumab in SLE subjects conducted in Japan **and** South Korea.
- **BEL113750: Only China subjects from the open-label portion of this Phase III, randomized, parallel group, double-blind study to evaluate the efficacy and safety of 10mg/kg belimumab intravenously at Weeks 0, 2, and 4, and then every 4 weeks, compared with placebo over a 52-week treatment period in subjects with active systemic lupus erythematosus (SELENA SLEDAI score \geq 8) in Northeast Asia.**
- HGS1006-C1066: An ongoing Phase III, open-label continuation study of parent study HGS1006-C1056 (BLISS 76), which enrolled and treated 268 SLE subjects with belimumab conducted in the United States

- LBSL99: An ongoing Phase II, open-label continuation study of parent study LBSL02, which enrolled and treated 296 SLE subjects with belimumab conducted in the United States and Canada.

Subjects eligible for inclusion in the treatment holiday group will have been treated with belimumab for at least 6 months in BEL114333 **or for at least 6 months in the BEL113750 open-label period for China subjects**, and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal.

Subjects eligible for inclusion in the control group will have been treated with belimumab for at least 6 months in BEL114333 **or for at least 6 months in the BEL113750 open-label period for China subjects**, and have a SELENA SLEDAI score ≤ 3 and complement (C3 and C4) levels at or above the central laboratory lower limit of normal but elect to continue their current treatment with belimumab 10 mg/kg.

Subjects eligible for inclusion in the long-term discontinuation group may have any level of SLE disease activity; will have been treated with belimumab for at least 6 months in any of the 3 continuation studies mentioned above, **or for at least 6 months in the BEL113750 open-label period for China subjects**; have discontinued belimumab therapy for no longer than 8 weeks prior to entry into this study and intend to remain off belimumab treatment for the 12 months of this study but to remain on standard of care therapy.

Subjects eligible for inclusion in the treatment holiday group will not be recruited from the long-term continuation studies LBSL99 or HGS1006-C1066, due to regulatory commitments for completing 10 years and 5 years on treatment, respectively. However, subjects who discontinue belimumab treatment in studies LBSL99 or HGS1006-C1066 can be recruited into the long-term discontinuation group in the present study.

For subjects entering the study, a minimum of 6 months previous participation in an open-label continuation studies **or China subjects in BEL113750 receiving open-label belimumab for at least 6 months**, will provide subjects initially randomized to placebo in parent studies with the opportunity to reach sufficient biological activity to achieve a belimumab pharmacological and/or clinical response.

The target sample size of 50 subjects in each of the treatment holiday and control groups is based on estimates of subject eligibility and number of subjects from continuation study **BEL114333 and China subjects in BEL113750 receiving open-label belimumab for at least 6 months**, is anticipated to provide consent to participate in this study. The target sample size of 35 subjects for the long-term discontinuation group is based on practical considerations of numbers of subjects anticipated to drop-out and not on statistical considerations.

Enrolment of subjects from the 3 belimumab continuation studies **or from the open-label period of BEL113750 for China subjects** into the long-term discontinuation group will remain open while recruitment to the treatment holiday and control groups is

ongoing or until 36 months have elapsed since study start. A target sample size of 35 subjects in the long-term discontinuation group is anticipated.

Because this study is non-randomized, subjects and investigators from study BEL114333 **and China subjects and China investigators from study BEL113750** will jointly decide upon which of the three groups to enrol into. Subjects recruited from the HGS1006-C1066 and the LBSL99 studies may only choose to enter the long-term discontinuation group, as they elect to no longer receive further belimumab therapy.

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750. This also makes the correction that China is not participating in the BEL114333 study,

Change 6: Inclusion Criteria

This change affects Section 4.2 Inclusion Criterion, All 3 subject groups, Criterion #1.

Change from:

Belimumab therapy: Received a minimum of 6 months therapy with belimumab 10 mg/kg in the continuation study BEL114333. Subjects in the long-term discontinuation group may additionally be recruited from continuation studies HGS1006-C1066 or LBSL99.

To:

Belimumab therapy: Received a minimum of 6 months therapy with belimumab 10 mg/kg in the continuation study BEL114333 **or from China subjects in BEL113750 who received open-label belimumab for at least 6 months.** Subjects in the long-term discontinuation group may additionally be recruited from continuation studies HGS1006-C1066 or LBSL99.

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 7: Inclusion Criteria

This change affects Section 4.2 Inclusion Criteria, control group, criterion #1.

Change from:

Belimumab therapy: Agree to continue receiving 10mg/kg belimumab intravenous infusions every 4 weeks. Subjects must be able to receive the first dose of belimumab in

this study 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in their previous continuation study.

To:

Belimumab therapy: Agree to continue receiving 10mg/kg belimumab intravenous infusions every 4 weeks. Subjects must be able to receive the first dose of belimumab in this study 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in their previous continuation study, **or the open-label period of BEL113750 for China subjects.**

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 8: Inclusion Criteria

This change affects Section 4.2 Inclusion Criteria, long-term discontinuation group, criterion #1.

Change from:

Continuation studies: Voluntarily withdrawn from continuation studies BEL114333, HGS1006-C1066, **or** LBSL99, and have withdrawn from belimumab therapy for no longer than 8 weeks prior to entry into this study.

To:

Continuation studies: Voluntarily withdrawn from continuation studies BEL114333, HGS1006-C1066, LBSL99, **or the open-label period of BEL113750 for China subjects**, and have withdrawn from belimumab therapy for no longer than 8 weeks prior to entry into this study.

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 9: Exclusion Criteria

This change affects Section 4.3 Exclusion Criteria, Any of the 3 subject groups, criterion #1.

Change from:

Undue risk: Have developed clinical evidence of significant, unstable or uncontrolled, acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases), or experienced an adverse event (AE) in the belimumab continuation studies BEL114333, HGS1006-C1066, **or** LBSL99 **studies**, that could, in the opinion of the principal investigator, put the subject at undue risk.

To:

Undue risk: Have developed clinical evidence of significant, unstable or uncontrolled, acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases), or experienced an adverse event (AE) in the belimumab continuation studies BEL114333, HGS1006-C1066, LBSL99, **or in the BEL113750 open-label period for China subjects**, that could, in the opinion of the principal investigator, put the subject at undue risk.

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 10: Study Treatments

This change affects Section 5.1 Study treatments, Investigational Product and Other Study Treatment, third paragraph.

Change from:

Subjects in the control group will receive belimumab 10 mg/kg IV infused for 1 hour every 28 days from Day 0 onwards. Subjects in this group must be able to receive their first dose of belimumab on Day 0 of this study 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the BEL114333 open-label continuation study.

To:

Subjects in the control group will receive belimumab 10 mg/kg IV infused for 1 hour every 28 days from Day 0 onwards. Subjects in this group must be able to receive their first dose of belimumab on Day 0 of this study 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the BEL114333 open-label continuation study, **or after the last dose from China subjects in the open-label period of BEL113750.**

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 11: Study Assessments and Procedures

This change affects Section 6, Study Assessments and Procedures, Time and Events Table (year 1) Table 2, footnote 2.

Change from:

The EXIT Visit in the respective feeder continuation studies will serve as the Day 0 visit for all 3 subject groups in this study. Assessments covered for both this study at Day 0 and the Exit visit of the feeder continuation studies need only be performed once and recorded in the appropriate case report forms for each study. Subjects in the control group must be able to receive the 1st dose of belimumab on Day 0 of this study on average 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the feeder continuation study.

To:

The EXIT Visit in the respective feeder continuation studies **and in the open-label period of BEL113750 for China subjects** will serve as the Day 0 visit for all 3 subject groups in this study. Assessments covered for both this study at Day 0 and the Exit visit of the feeder continuation studies **and the open-label period of BEL113750 for China subjects** need only be performed once and recorded in the appropriate case report forms for each study. Subjects in the control group must be able to receive the 1st dose of belimumab on Day 0 of this study on average 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the feeder continuation study **and in the open-label period of BEL113750 for China subjects**.

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 12: Study Assessments and Procedures

This change affects Section 6, Study Assessments and Procedures, Time and Events Table (year 1) Table 2, footnote 4.

Change from:

For subjects in the control group only, obtain written informed consent to participate in this study at the visit prior to the last visit in the relevant SLE feeder continuation study.

To:

For subjects in the control group only, obtain written informed consent to participate in this study at the visit prior to the last visit in the relevant SLE feeder continuation study **and the open-label period of BEL113750 for China subjects.**

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 13: Study Assessments and Procedures

This change affects Section 6, Study Assessments and Procedures, Time and Events Table (year 1) Table 2, footnote 10.

Change from:

PGx sampling from consenting subjects recruited from all studies except from study BEL114333. PGx informed consent must be obtained prior to sampling.

To:

PGx sampling from consenting subjects recruited from all studies except from study BEL114333 **and except from the open-label period of BEL113750 for China subjects.** PGx informed consent must be obtained prior to sampling.

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 14: Endpoints

This change affects Section 6.1.2 Endpoints, Secondary Endpoints, Note:

Change from:

Note: baseline is the time before any treatment with belimumab, which was Day 0 of the original parent studies that fed into the 3 continuation studies, from which subjects were recruited into this study. When Day 0 is used in relation to endpoints, this refers to Day 0 of this study.

To:

Note: baseline is the time before any treatment with belimumab, which was Day 0 of the original parent studies that fed into the 3 continuation studies, **and Day 0 of the blinded period of BEL113750 for China subjects**, from which subjects were recruited into this study. When Day 0 is used in relation to endpoints, this refers to Day 0 of this study.

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 15: Critical Baseline Assessments

This change affects Section 6.2 Critical Baseline Assessments, second and third Paragraphs.

Change from:

The EXIT visit of the relevant SLE continuation protocol ((BEL114333, HGS1006-C1066, or LBSL99) from which the subject is recruited will serve as the Day 0 visit in this study. Subjects in the control group will be dosed with belimumab at the Day 0 visit as part of this protocol. These subjects must be able to receive the Day 0 dose in this study 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the previous open-label continuation study. Any procedures from this protocol or from the relevant previous open-label continuation protocols to be performed pre-dose must be completed before dosing subjects in the control group. Subjects in the control group should sign the informed consent to participate in this study at the visit immediately prior to the EXIT visit to ensure a supply of belimumab for the Day 0 visit in this study. Subjects in the treatment holiday and long-term discontinuation groups should sign the informed consent at the screening visit and Day 0 visit, respectively of this study.

Procedures necessary for the Day 0 visit of this protocol and for the last visit of the relevant SLE open-label continuation protocol from which the subject is recruited need only be performed once. Results from Day 0 procedures that are duplicated in the relevant SLE continuation study will be recorded in the eCRF for that study and must also be transcribed to the relevant eCRFs in this study. Additional Day 0 procedures exclusive to this study will be recorded directly in the eCRFs for this study.

To:

The EXIT visit of the relevant SLE continuation protocol ((BEL114333, HGS1006-C1066, or LBSL99), **or the open-label period of BEL113750 for China subjects**, from which the subject is recruited will serve as the Day 0 visit in this study. Subjects in the control group will be dosed with belimumab at the Day 0 visit as part of this protocol. These subjects must be able to receive the Day 0 dose in this study 4 weeks (minimum of

2 weeks, maximum of 8 weeks) after the last dose in the previous open-label continuation study, **or the open-label period of BEL113750 for China subjects**. Any procedures from this protocol or from the relevant previous open-label continuation protocols, **or the open-label period of BEL113750 for China subjects** to be performed pre-dose must be completed before dosing subjects in the control group. Subjects in the control group should sign the informed consent to participate in this study at the visit immediately prior to the EXIT visit to ensure a supply of belimumab for the Day 0 visit in this study. Subjects in the treatment holiday and long-term discontinuation groups should sign the informed consent at the screening visit and Day 0 visit, respectively of this study.

Procedures necessary for the Day 0 visit of this protocol and for the last visit of the relevant SLE open-label continuation protocol, **or the open-label period of BEL113750 for China subjects**, from which the subject is recruited need only be performed once. Results from Day 0 procedures that are duplicated in the relevant SLE continuation study will be recorded in the eCRF for that study and must also be transcribed to the relevant eCRFs in this study. Additional Day 0 procedures exclusive to this study will be recorded directly in the eCRFs for this study.

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 16: SELENA SLEDAI

This change affects Section 6.3.1.1 SELENA SLEDAI Score, Scoring for Proteinuria at Screening for Eligibility, first sentence.

Change from:

The proteinuria score for SELENA SLEDAI must be 0 at the most recent assessment performed in BEL114333.

To:

The proteinuria score for SELENA SLEDAI must be 0 at the most recent assessment performed in BEL114333 **or in the open-label period of BEL113750 for China subjects**.

Rationale:

Clarifies that China subjects will be recruited from the open-label period of study BEL113750.

Change 17: SELENA SLEDAI

This change affects Section 6.3.1.2 Laboratory tests for SELENA SLEDAI, last sentence.

Change from:

Values outside the reference laboratory normal range **that** require the investigator's assessment of relationship to SLE:

To:

Values outside the reference laboratory normal range require the investigator's assessment of relationship to SLE.

Rationale:

Correction of typographical error.

Change 18: Safety

This change affects new Section 6.4.1.1, Liver Chemistry Stopping and Follow up Criteria, Additional Hepatitis B Monitoring.

Add:

Additional Hepatitis B Monitoring

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

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

Rationale:

Additional hepatitis B monitoring was included in the BEL113750 China specific protocol amendment 04, which included obtaining a new HBV DNA test during the study, for China subjects with screening reactive anti- HBc but negative screening HBV DNA who enrolled, but found to have an ALT and/or AST elevation of 2.5 x ULN as part

of the new hepatitis B exclusion criterion #17 change in that protocol. China subjects recruited from the open-label period of BEL113750 will continue to have this additional hepatitis B monitoring in this study BEL116027.

Change 19: Pharmacogenetic Research

This change affects Section 6.7 Pharmacogenetic Research, first paragraph.

Change from:

Collect a blood sample for pharmacogenetics (PGx) from consenting subjects except those recruited from Study BEL114333 (who have already provided a sample as part of that study). Samples for PGx must be drawn prior to dosing as appropriate.

To:

Collect a blood sample for pharmacogenetics (PGx) from consenting subjects except those recruited from Study BEL114333 **and except from the open-label period of BEL113750 for China subjects** (who have already provided a sample as part of that study). Samples for PGx must be drawn prior to dosing as appropriate.

Rationale:

Obtaining PGx samples has already been addressed for subjects that have participated in studies BEL114333 and BEL113750 and PGx samples do not need to be obtained in the BEL116027 study.

Change 20: Appendix 5: Clinical Laboratory Tests

This change affects Section 11.5, Appendix 5, Clinical Laboratory Tests.

Add:

Hepatitis B Viral DNA PCR Quantitative (HBV DNA), BLYS Protein, ANA, aCL

Rationale:

Provide consistency of laboratory tests with the parent/feeder China specific BEL113750 protocol amendment 04.