TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	BEL114333, a multicenter, continuation study of belimumab in subjects with systemic lupus erythematosus (SLE) who completed the phase III study BEL113750 in Northeast Asia or completed the open-label extension of HGS1006-C1115 in Japan

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
YM2010/00145/00	2011-NOV-18	Original
YM2010/00145/01	2012-MAR-27	Amendment No. 1
Addition of inadvertently omitted sentence in Protocol Summary Study Design Section Addition in Section 4.2 Inclusion Criteria of supplemental birth control recommendation for subjects taking MMF Modification of Section 4.4 Withdrawal Criteria redundant item Modification of Section 5 for the addition of a 3-hour clinical supervision time after subjects receive the first 2 infusions Addition of footnote to Section 6 Time and Events Table (Year 1 only) for 3-hour clinical supervision after subjects receive the first 2 infusions Addition of footnote to Section 6 Time and Events Table (Additional Years) for Laboratory Test clarification Modification of Section 6.3.9 for the addition of a 3-hour clinical supervision time after subjects receive the first 2 infusions Deletion of 2 clinical laboratory tests in Appendix 5 inadvertently listed Correction of minor typographical errors and consistency errors		
YM2010/00145/02	2012-JUL-17	Amendment No. 2
Addition of Protocol Summary Study Design B-cell subset labs Modification of Protocol Summary Study Design immunogenicity labs at 6 months post last dose Clarification of Protocol Summary Study Endpoint/Assessments for B-cell subsets at selected sites Modification of Section 3.1 immunogenicity labs at 6 months post last dose Clarification of Section 3.1 for B-cell subsets lab collection times at selected sites Modification of Section 4.4 immunogenicity and B-cell subsets labs at 6 months post last dose Modification of Section 5 immunogenicity and B-cell subsets labs at 6 months post last		

dose Addition of Section 6 Time and Events Table, Year 1 and Additional Years, B-cell marker labs at Week 48 Modification of Section 6 Time and Events Table, Year 1 and Additional Years, immunogenicity labs at 6 months post last dose in footnotes Addition of Section 6 Time and Events Table, Year 1 and Additional Years, B-cell subsets at selected sites in footnotes Clarification of Section 6.1.1 for B-cell subsets collected only at selected sites Addition and clarification of Section 6.3 B-cell markers at Week 48 and at selected sites Modification of Section 6.3 immunogenicity labs at 6 months post last dose Modification of Section 6.3.13.1 immunogenicity labs at 6 months post last dose Clarification of Section 6.4 for B-cell subsets collected only at selected sites		
YM2010/00145/03	2014-MAY-16	Amendment No. 3
Changes were made to the following sections to allow subjects who complete the open-label SC extension of C1115 in Japan the option of continuing treatment with IV belimumab, as an add-on to their standard of care SLE therapy: Modification of Study Title Modification of Protocol Summary Rationale and Study Design Addition of new heading Section 1.3.1, “Belimumab Administered Intravenously” Addition of new section Section 1.3.2, “Belimumab Administered Subcutaneously” Modification of Section 1.4, Rationale Modification of Section 3.1, Study Design Modification of Section 3.2, Discussion of Design Modification of Section 4.1, Number of Subjects Modification of Section 4.2, Inclusion Criteria Modification of Section 4.3, Exclusion Criteria Modification of Section 5, Study Treatments Modification of Section 5.4, Treatment after the End of the Study		

Modification of Section 6 Time and Events Table, Column headings for first 2 columns, and footnote 1

Modification of Section 6 Time and Events Table Additional Years, footnote 3

Modification of Section 6.1, Critical Baseline Assessments

Modification of Section 6.1.1, Procedures (Day 0)

Modification of Section 6.2.1.2, Secondary Endpoints

Modification of Section 7, Data Management

Modification of Section 8.1.1, Primary Efficacy Analysis

Modification of Section 8.1.2, Analysis of Additional Efficacy and Biomarkers

Modification of Section 8.1.3, Analysis of Safety Variables

Modification of Section 9.5, Study Site Closure

Updating of Section 10, References

Updating of Progressive Multifocal Leukoencephalopathy wording to reflect new information received by the Sponsor:

Modification of Section 6.3.10.1, Progressive multifocal leukoencephalopathy.

Modification of Section 6.2.13.2 to reflect current methods

Change to Appendix 7:

Addition of sub-headings for each protocol amendment for clarification

SPONSOR SIGNATORY

PPD

5/16/2014 (16-May-2014)

David A. Roth, MD, MSCE

Date

Director, Global Clinical R&D,
Immuno-Inflammation Therapy Area

SPONSOR INFORMATION PAGE

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Regulatory Agency Identifying Number(s): N/A

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number BEL114333

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

aCL	Anticardiolipin
ACE	Angiotensin-converting enzyme
ACR	American College of Rheumatology
AE	Adverse Event
ALT	alanine amininotransferase
ANA	anti-nuclear antibody
ANCOVA	Analysis of Covariance
AST	aspartate aminotransferase
BILAG	British Isles Lupus Assessment Group
BLyS	B lymphocyte Stimulator
CBC	Complete blood count
CNS	Central Nervous System
CPK	Creatinine phosphokinase
CrCl	Creatinine clearance
CRF	Case report form
C-SSRS	Columbia Suicidality-Severity Rating Scale
CVA	Cerebrovascular accident
dL	decilitre
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
dsDNA	double stranded DNA
ECG	Electrocardiogram
ECL	electrochemiluminescence
eCRF	electronic case report form
ELISA	enzyme linked immunosorbent assay
FACS	florescence activated cell sorting
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular filtration rate
GSK	GlaxoSmithKline
HB	Hepatitis B
HBsAg	Hepatitis B surface antigen
HBc	Hepatitis B core
HEp-2	Human Epithelial Cell Line 2
HGS	Human Genome Sciences, Inc
hpf	High power field
IB	Investigator's Brochure
IEC	Independent ethics committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-6	Interleukin-6
IM	Intramuscular
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine device

IUS	Intrauterine system
IV	Intravenous
IVIG	Intravenous immunoglobulin
IVRS	Interactive voice response system
kg	kilogram
LDH	lactate dehydrogenase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	milligram
MITT	Modified intent to treat
mL	millilitre
MMF	Mycophenolate mofetil
MSD	Meso Scale Discovery
MSDS	Materials Safety Data Sheet
NR	Nonresponder
NSAIDs	non-steroidal anti-inflammatory drugs
PCR	polymerase chain reaction
PGA	Physician's Global Assessment
PGx	Pharmacogenetics
PK	Pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PO	By mouth (per os)
PT	prothrombin time
PTT	partial thromboplastin time
RA	rheumatoid arthritis
RAP	Reporting and Analysis Plan
RBC	red blood cell
RF	Rheumatoid factor
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SC	Subcutaneous
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
SOCs	System Organ Classes
SPM	Study Procedures Manual
SRI	SLE Responder Index
SWFI	Sterile water for injection
TACI Fc	transmembrane activator attached to the Fc portion of an immunoglobulin
TF	Treatment Failure
TNF	Tumour Necrosis Factor
ULN	Upper limit of normal
VAS	Visual analogue scale

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PROTOCOL SUMMARY

Rationale

This study provides subjects who complete the BEL113750 Study in Northeast Asia and subjects who complete the open-label extension of HGS1006-C1115 (referred to as C1115) Study in Japan the option of receiving belimumab, as an add-on to their standard of care (SOC) SLE therapy. All eligible subjects will receive belimumab 10 mg/kg irrespective of their randomized treatment in BEL113750 or C1115. This is an optional study in which eligible subjects will be enrolled at the discretion of the investigator and consent of the subject. The study will also provide data on long-term safety and efficacy of belimumab in Northeast Asia.

Objective(s)

Primary Objective

The primary objective is to evaluate long-term safety and tolerability of belimumab in subjects with SLE in Northeast Asia.

Secondary Objective

The secondary objective is to evaluate the long-term efficacy of belimumab in subjects with SLE in Northeast Asia.

Study Design

This is a multicentre, continuation study of belimumab plus SOC in SLE subjects who completed the Phase III BEL113750 protocol in Northeast Asia or who completed the open-label extension of the C1115 protocol in Japan. Subjects participating in this protocol will continue to be monitored for safety and efficacy.

Subjects will give written informed consent before any study procedures are performed. Subjects will be reconsented whenever new information becomes available that may affect their willingness to participate in the study.

Subjects who complete 48 weeks of treatment on the BEL113750 or complete the open-label extension of C1115 and who meet inclusion/exclusion criteria, will be given the option to enter the continuation study. All subjects will receive belimumab 10 mg/kg IV infused over 1 hour every 28 days. The first dose on the continuation study must be given 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750. For subjects enrolling from C1115, the target for the first dose of IV belimumab is 1 week after the last dose of SC belimumab (scheduled for Week 23 in the open-label extension). The EXIT visit of the C1115 study (Week 24) serves as the Day 0 visit for the Protocol BEL114333, and will have a +1 week visit window. All subjects will continue therapies as prescribed by the investigator. However, subjects who start prohibited medications or therapies at any time during the study must be withdrawn from treatment with belimumab and will enter study follow-up. (See Section 5.3.2 and Section 5.3.3).

Clinical laboratory evaluations (haematology, chemistry and urinalysis), will occur 4 weeks (28 days), 12 weeks (84 days), 24 weeks (168 days), 36 weeks (252 days), and 48 weeks (336 days) after the first dose of study medication in this protocol, then every 24 weeks thereafter, and at the Exit visit and the Week 16 follow-up visit. Serum IgG will be evaluated at 12 weeks (84 days), 24 weeks (168 days) and 48 weeks (336 days) after the first dose of study medication and then every 48 weeks thereafter and at the Exit visit and the Week 16 follow-up visit. Serum IgA and IgM will be evaluated in this protocol at Week 0 and Week 48, and then every 48 weeks thereafter and at the Exit visit. Adverse events will be assessed at every visit except at the 6 month follow-up visit. Subjects should be clinically evaluated by their investigating physician at each visit. It is the investigator's responsibility to manage their patient's SLE as necessary. Complete efficacy evaluations (SELENA SLEDAI, BILAG, SLE Flare Index along with PGA) and evaluation of biomarkers will occur every 24 weeks (168 days). B-cell subsets will be collected at Week 48, the EXIT visit, and at approximately 6 months after the last dose of study agent, from subjects at selected sites only.

During the course of the study, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate in response to improving or worsening conditions. Prohibited medications in this study are similar to BEL113750 and C1115. Subjects who start prohibited medications or therapies (see Section 5.3.2 and Section 5.3.3) at any time during the study must be withdrawn from treatment with belimumab and enter study follow-up. After discontinuation of study medication, subjects will return for an Exit visit 4 weeks after the last study medication administration and for a follow up visit at 16 weeks after the last dose of study medication. For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent. Withdrawal of subjects from treatment and the procedures to be followed are described in Section 4.4.

Subjects recruited into this study will continue to receive treatment with intravenous belimumab until such time as intravenous belimumab becomes commercially available in a subject's country of participation, 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.

The maximum number of subjects enrolled in this study will not exceed the maximum number of subjects enrolled and randomized in Protocol BEL113750 plus the number of subjects from Japan from the open-label extension of the C1115 study.

A subject will be regarded as having completed the study if the subject is still participating in the study at the time intravenous belimumab becomes commercially available in a subject's country of participation, or upon the decision by the sponsor to discontinue the study.

Study Endpoints/Assessments

The primary efficacy endpoint is a composite response rate at each scheduled visit when complete efficacy evaluations occur (e.g., Weeks 24 and 48 of Year 1 and Year 2, etc), consisting of

- ≥ 4 point reduction from baseline in SELENA SLEDAI score, AND
- No worsening (increase of < 0.30 points from baseline) in Physician's Global Assessment (PGA), AND
- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Week 52).

All other endpoints will be derived from the following assessments: SELENA SLEDAI, PGA, BILAG, SLE Flare Index, prednisone dose, renal flare assessment, proteinuria, biomarkers (immunoglobulins, complement, anti-dsDNA autoantibodies, and B cell subsets (at selected sites)), immunogenicity, adverse events, clinical laboratory assessments (clinical chemistry and haematology) and plasma levels of belimumab.

1. INTRODUCTION

1.1. Disease Background Relevant to Clinical Study

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.

A clinical diagnosis of SLE includes features that are thought to involve dysregulation of B lymphocytes [Liossis, 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.

Patients with SLE have about a 3-fold greater risk of mortality than the general population. Approximately 70% of SLE patients survive 20 years from time of diagnosis [Houssiau, 2004]. Standard therapies for SLE include corticosteroids (the mainstay of therapy), anti-malarial agents (e.g., hydroxychloroquine), non-steroidal anti-inflammatory drugs (NSAIDs), cytotoxic agents like cyclophosphamide, and immunosuppressive/immunomodulatory agents (e.g., azathioprine, cyclosporine, mycophenolate mofetil (MMF), methotrexate, leflunomide, thalidomide, 6-mercaptopurine) [Petri, 2001; Reveille, 2001; Ginzler, 2005; Houssiau, 2004; Ruiz-Irastorza, 2001; Wallace, 2002; Brocard, 2005; Chatham, 2001]. Although active lupus nephritis and CNS vasculitis can usually be controlled with several courses of high dose steroids and cyclophosphamide over a 1 to 2 year period, there tends to be progressive relapsing of disease over time [Petri, 2001; Houssiau, 2002; Illei, 2001; Ruiz-Irastorza, 2001]. These therapies can be associated with significant toxicity. Long-term use of high-dose corticosteroids can cause significant morbidity including osteoporosis, osteonecrosis, metabolic disorders (including exacerbation of diabetes), increased infection risk, edema, weight gain and hyperlipidemia [Chatham, 2001]. Cytotoxic agents like cyclophosphamide are immunosuppressive, resulting in increased risk of serious infections and certain cancers.

The prevalence of SLE in Hong Kong & mainland China was found to range from 58.8/100,000 to 73.3/100,000 in two studies [Mok, 2003; Xiang, 2009]. When compared with US SLE prevalence estimates of 100.0/100,000 [Naleway, 2005; Chakravarty, 2007], SLE disease burden does not appear to be higher in China. Conversely, SLE prevalence in the EU 5 regions (UK, Germany, France, Spain, and Italy) was estimated at 43.0/100,000 [Govoni, 2006; Lopez, 2003; Nightingale, 2006] which is lower than in China. Regarding disease activity, Boers [Boers, 2006] reported more severe SLE among Asian patients admitted to a medical centre in Australia, with Southeastern Asian/Chinese

patients having a median Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) of 13 at first admission compared to a median SLEDAI of 8 among Caucasians.

1.2. Belimumab

The trade name of the investigational product is BENLYSTA (also known as Lymphostat-B). The generic (USAN/INN) name is belimumab.

1.2.1. Mechanism of Action

Belimumab, (also known as LymphoStat-B; BENLYSTA), developed by Human Genome Sciences (HGS), 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).

1.3. Clinical Experience with Belimumab

1.3.1. Belimumab Administered Intravenously

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

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

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

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

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

1.3.2. Belimumab Administered Subcutaneously

A subcutaneous (SC) liquid formulation of belimumab has been developed and is currently in a Phase 3 trial (Protocol HGS1006-C1115, referred to as C1115).

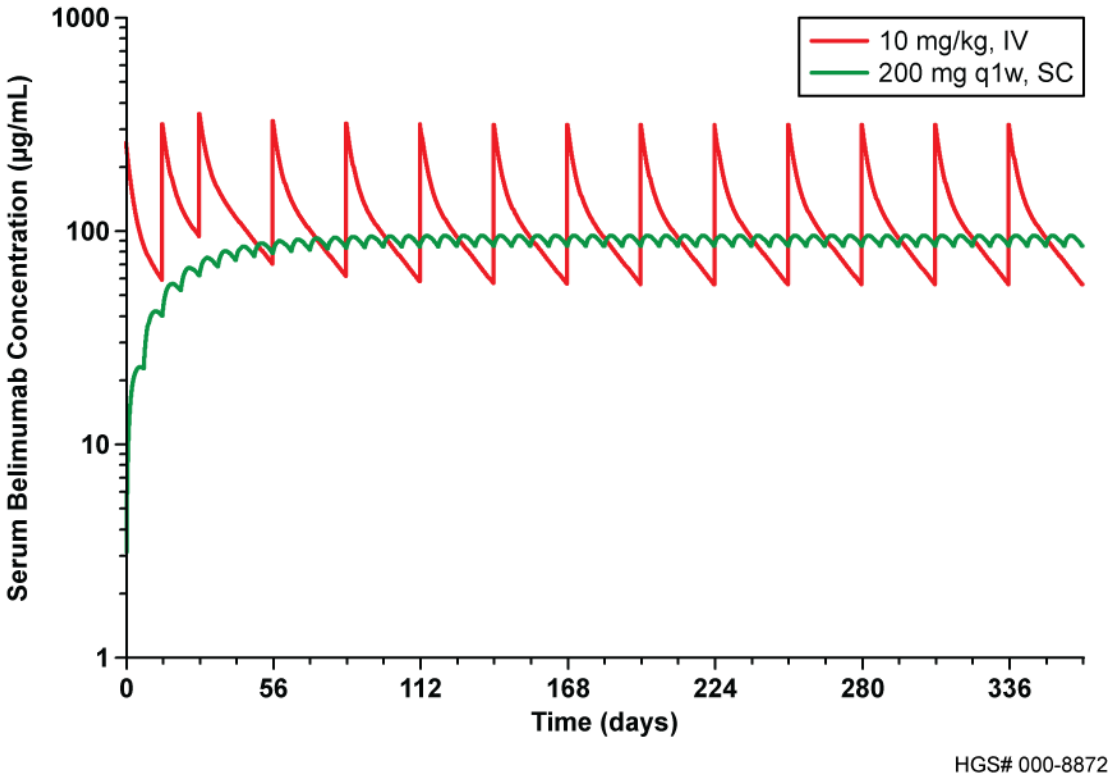
Based on PK data from the Phase 1 SC study (Protocol HGS1006-C1105, referred to as C1105), subjects given belimumab (200 mg/mL) 200 mg SC every week are expected to achieve on average similar steady-state AUC levels compared to those observed in the IV Phase 3 trials with 10 mg/kg IV every 4 weeks.

In the Phase 3 study, patients self-administer a fixed dose of 200 mg belimumab as an SC injection. Due to the relatively slow absorption from the subcutaneous to the central compartment, maximal serum belimumab concentrations following SC administration are not expected to exceed those observed following IV administration in the Phase 3 trials even for lower weight subjects (Figure 1).

Safety data for SC administration have been generated in a 24-week Phase 2 study using the original 100 mg/mL SC formulation in SLE patients (Protocol HGS1006-C1070, referred to as C1070). Although the number of subjects is small (N = 28), a dose of 300 mg weekly (100 mg SC 3x/wk) was generally well-tolerated (Study C1070, see Investigator's Brochure). In healthy Japanese male subjects, a single 200 mg SC dose vs a single IV dose of belimumab were evaluated in terms of safety and PK (BEL116119, see Investigator's Brochure). The bioavailability of the single SC dose of 200 mg belimumab in the subjects was estimated to be 77.5%. Geometric mean terminal half-life after single SC administration was 15.9 days which was comparable to the 17.7 days observed after single IV administration. All 7 AEs were mild or moderate in intensity. One event (cellulitis) reported in the IV group was judged to be related to the belimumab. No SAEs or AEs related to injection site reactions were reported during the study. [Shida, 2014]. Four weekly SC doses of belimumab at 2x120 or 200 mg were evaluated in

healthy subjects in terms of safety and PK in Study C1105 and have been generally well tolerated.

Figure 1 Comparison of simulated mean belimumab serum concentration time profile with 10 mg/kg IV on days 0, 14, and 28 and Q4 weeks thereafter with simulated profile of 200 mg weekly SC



10 mg/kg IV data simulated using PK parameters from population PK analysis in SLE patients (HGS1006-POPPK); SC profile simulated using PK parameters from Study C1105 in healthy subjects.

The ongoing Phase 3 trial of SC belimumab in SLE patients (C1115) has completed enrollment with 839 patients as of 10 February 2014. The independent Data and Monitoring Committee reviews data from this study every 6 months; the most recent review was 29 October 2013 and no changes were recommended.

1.4. Rationale

This study provides subjects who complete the BEL113750 Study in Northeast Asia or subjects from Japan who complete the open-label extension of C1115 the option of receiving belimumab, as an add-on to their standard of care (SOC) SLE therapy. All eligible subjects will receive belimumab 10 mg/kg irrespective of their randomized treatment in BEL113750 or C1115. This is an optional study in which eligible subjects will be enrolled at the discretion of the investigator and consent of the subject. The study will also provide data on long-term safety and efficacy of belimumab.

Belimumab (also known as LymphoStat-B; BENLYSTA) 10 mg/kg administered IV was approved on 09 March 2011 in the United States (US), on 06 July 2011 in Canada,

and on 13 July 2011 in the European Union (EU) for the treatment of adult patients with active autoantibody-positive SLE who are receiving standard therapy.

2. OBJECTIVE(S)

2.1. Primary Objective

The primary objective is to evaluate long-term safety and tolerability of belimumab in subjects with SLE in Northeast Asia.

2.2. Secondary Objective

The secondary objective is to evaluate the long-term efficacy of belimumab in subjects with SLE in Northeast Asia.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a multicentre, continuation study of belimumab plus SOC in SLE subjects who completed the Phase III BEL113750 protocol in Northeast Asia and subjects who completed the open-label extension of C1115 in Japan. Subjects participating in this protocol will continue to be monitored for safety and efficacy. The frequency of safety laboratory evaluations has been reduced in this protocol compared with BEL113750 and C1115 based on the safety profile of belimumab studies to date and is not anticipated to compromise the well being and safety of subjects.

Subjects must give written informed consent before any study procedures are performed. Subjects will be reconsented whenever new information becomes available that may affect their willingness to participate in the study.

Subjects who complete 48 weeks of treatment on the BEL113750 study or complete the open-label extension of C1115 and who meet inclusion/exclusion criteria, and provide informed consent, will be given the option to enter the continuation study. All subjects will receive belimumab 10 mg/kg IV infused over 1 hour every 28 days. The first dose on the continuation study must be given 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750. For subjects enrolling from C1115, the target for the first dose of IV belimumab is 1 week after the last dose of SC belimumab (scheduled for Week 23 in the open-label extension). The EXIT visit of the C1115 study (Week 24) serves as the Day 0 visit for the Protocol BEL114333, and will have a +1 week visit window. All subjects will continue therapies as prescribed by the investigator. During the course of the study, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate in response to improving or worsening conditions. However, subjects who start prohibited medications or therapies (see Section 5.3.2 and Section 5.3.3) at any time during the study must be withdrawn from treatment with belimumab and enter study follow-up. After discontinuation of belimumab, subjects will return for an Exit visit 4 weeks after the last study medication administration and for follow up visit at 16 weeks after the last

dose of belimumab. For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent. Withdrawal of subjects from treatment and the procedures to be followed are described in Section 4.4.

Clinical laboratory evaluations (haematology, chemistry and urinalysis), will occur 4 weeks (28 days), 12 weeks (84 days), 24 weeks (168 days), 36 weeks (252 days), and 48 weeks (336 days) after the first dose of study medication on this protocol, then every 24 weeks thereafter and at the Exit visit and the Week 16 follow-up visit. Serum IgG will be evaluated at 12 weeks (84 days), 24 weeks (168 days) and 48 weeks (336 days) after the first dose of study medication and then every 48 weeks thereafter and at the Exit visit and the Week 16 follow-up visit. Adverse events will be assessed at every visit except at the 6 month follow-up visit. Subjects should be clinically evaluated by their investigating physician at each visit. It is the investigator's responsibility to manage their patient's SLE as necessary. Complete efficacy evaluations (SELENA SLEDAI, BILAG, SLE Flare Index along with PGA) and evaluation of biomarkers will occur every 24 weeks (168 days). B-cell subsets will be collected at Week 48, the EXIT visit, and at approximately 6 months after the last dose of study agent, from subjects at selected sites only.

Subjects recruited into this study will continue to receive treatment with intravenous belimumab until such time as intravenous belimumab becomes commercially available in a subject's country of participation, 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.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential.

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.

A subject will be regarded as having completed the study if the subject is still participating in the study at the time intravenous belimumab becomes commercially available in a subject's country of participation, or upon the decision by the sponsor to discontinue the study.

3.2. Discussion of Design

The BEL113750 study design was based on 2 global, Phase III clinical trials (HGS1006-C1057 and HGS1006-C1056) which demonstrated that subjects treated with belimumab had a statistically significantly better response rate at the primary endpoint at week 52, than those treated with placebo. BEL114333 provides subjects who complete the BEL113750 study the option of continuing treatment with belimumab for those randomized to belimumab, or the option to begin treatment with belimumab for those

randomized to placebo, as an add-on to their standard of care SLE therapy. Subjects who completed 48 weeks of treatment and return for the final 52-week evaluation on BEL113750 may be recruited into this continuation protocol of open-label belimumab. BEL114333 provides subjects who complete the open-label SC extension of C1115 in Japan the option of continuing treatment with IV belimumab, as an add-on to their standard of care SLE therapy.

This study will continue until the subject withdraws from the trial, or intravenous belimumab becomes commercially available in the relevant participating country, or the subject elects to participate in another belimumab continuation study for SLE, or upon the decision by the sponsor to discontinue development/marketing of belimumab for SLE.

In the Phase II and Phase III continuation trials, the incidence rates of adverse events (AEs) in general and by SOCs (including infections), serious AEs, and malignancies were comparable to placebo per 100 subject years of exposure. The overall incidence rate of adverse events remained stable or decreased over 6 years of exposure to belimumab. GlaxoSmithKline (GSK) will remain blinded to subjects' treatment until all data from the Phase III study, BEL113750, are locked and unblinded. Clinical sites will remain blinded to previous treatment on BEL113750 until after the results of BEL113750 are publicly disclosed.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

The maximum number of subjects enrolled in this study will not exceed the maximum number of subjects enrolled and randomized in Protocol BEL113750 in Northeast Asia plus the number of subjects from Japan in the open label extension of the C1115 study.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on belimumab that may impact subject eligibility is provided in the Investigator Brochure (IB).

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 the study must meet all of the following criteria:

1. Have completed the BEL113750 Protocol in Northeast Asia through Week 48 OR have completed the open-label extension of C1115 in Japan.
2. Be able to receive the first dose of belimumab for BEL114333 four weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750 OR be able to receive the first dose of IV belimumab 1 week (plus a 1 week visit window) after the last dose of open-label SC belimumab in C1115.

3. A female subject not pregnant or nursing 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 screening, and agree to one of the following:

     - Complete abstinence from penile-vaginal intercourse, when this is the female's preferred and usual lifestyle, from 2 weeks prior to administration of the first dose of belimumab until 16 weeks after the last dose of belimumab; or

     - Consistent and correct use of one of the following acceptable methods of birth control for 1 month prior to the start of belimumab and for 16 weeks after the last dose of belimumab:

       - 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).

4.3. 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 the study:

1. 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 respective Phase 3 studies that could, in the opinion of the principal investigator, put the subject at undue risk.
2. 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.

4.4. Withdrawal Criteria

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue a subject from this study. Every effort should be made by the investigator to keep subjects in the study and to ensure return for the Exit visit 4 weeks after the last dose of belimumab, and the follow-up visits 16 weeks after the last dose. For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent. From subjects at selected sites only, B-cell subsets will be collected at the EXIT visit and at approximately 6 months after the last dose of study agent.

Notwithstanding this requirement, the investigator should adjust concurrent medications as clinically required.

Reasons for subject withdrawal include “adverse event”, “lack of efficacy”, “protocol deviation”, “study closed/terminated”, “lost to follow-up”, “investigator discretion”, and “withdrew consent”. The investigator will record the primary reason in the electronic case report form (eCRF) and any data collected up until the point of withdrawal, and the follow-up visits will be used in the analyses.

If a subject is permanently discontinued from belimumab during the course of the study, the subject must be withdrawn from the study. In addition, subjects will be withdrawn from the study if any of the following criteria are met:

- **Unacceptable toxicity** including:
  - **Laboratory parameters:** Demonstrate clinically important changes in laboratory parameters.
  - **Liver Chemistry:** Detailed in Section 6.3.1.
- **Pregnancy:** Positive urine pregnancy test.
- **Concurrent Medication:** Prohibited concurrent medication or therapy (See Section 5.3.2 and Section 5.3.3).
- **Consent:** Withdrawal of consent.
- **Compliance:** Missed 3 or more consecutive study infusions.

5. STUDY TREATMENTS

A summary of the characteristics of belimumab is presented 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	400mg per vial (to contain 80mg/mL when reconstituted with 4.8mL sterile water for injection [SWFI])
Physical description	White uniform lyophilised cake in a 20mL vial
Manufacturer	Human Genome Sciences, Inc.
Route of administration	Intravenous

The contents of the label will be in accordance with all applicable regulatory requirements.

Under normal conditions of handling and administration, belimumab 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. Access to and administration of belimumab will be limited to the investigator and authorised site staff. Maintenance of a temperature log (manual or automated) is required. Belimumab must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

All used belimumab vials should be destroyed 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.

Belimumab for injection will be supplied in glass and labelled in accordance with all applicable regulatory requirements. The belimumab IV solution should be made up by a pharmacist.

The 400 mg single use vial of belimumab will be reconstituted with 4.8 mL sterile water for injection, to yield a final concentration of 80 mg/mL of belimumab. 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 reconstituted belimumab will be diluted in 250 mL normal saline for IV infusion. An amount of normal saline, equal to the calculated amount of belimumab to be added, should be removed from the infusion bag prior to adding the belimumab. After adding the reconstituted belimumab, gently invert the bag to mix the solution. The prepared belimumab should be infused over 1 hour.

Refer to the Pharmacy Manual for detailed instructions on the preparation, administration, and storage of belimumab.

The first dose on the continuation trial must be given 4 weeks (minimum 2 weeks, maximum 8 weeks) after the last dose in BEL113750. For subjects enrolling from C1115, the target for the first dose of IV belimumab is 1 week after the last dose of SC belimumab (scheduled for Week 23 in the open-label extension). The EXIT visit of the C1115 study (Week 24) serves as the Day 0 visit for the Protocol BEL114333, and will have a +1 week visit window. All subjects will receive belimumab 10 mg/kg IV infused over 1 hour every 28 days.

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

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. Otherwise, subjects will be monitored during and after each infusion according to study sites' guidelines or standard operating procedure for IV infusions. This may include, but is not limited to, monitoring vital signs and observing for any untoward reactions.

Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Trained rescue personnel and rescue medications/equipment should be available for a minimum of the first 2 doses. 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), administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions should be considered. If a 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, the investigator may delay the dose by up to 2 weeks or withhold 1 dose. If a similar concern is present at the time of the next scheduled dose, the investigator should contact the Medical Monitor to determine whether treatment with belimumab should be discontinued.

If a subject experiences a clinically significant, potentially life-threatening (Grade 4) AE that in the clinical judgement of the investigator is possibly, probably or definitely related

to belimumab then treatment with belimumab will be discontinued. The subject should be withdrawn from the study and followed at regularly scheduled monthly study visits as required until resolution of the AE(s) and must also return for follow-up at the EXIT visit 4 weeks after the last dose of belimumab, and the follow-up visit 16 weeks after the last dose. For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent. From subjects at selected sites only, B-cell subsets will be collected at the EXIT visit and at approximately 6 months after the last dose of study agent.

5.1. 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 belimumab 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.

5.2. 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).

If a subject misses 3 or more consecutive study infusions, they will be withdrawn from the study (See Section 4.4).

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

5.3. Concomitant Medications and Non-Drug Therapies

This section reviews the medications allowed and prohibited during the course of the study. Subjects who start prohibited medications or therapies (see Section 5.3.2 and Section 5.3.3) will be withdrawn from treatment with belimumab and enter protocol required follow-up.

5.3.1. Permitted Medications and Non-Drug Therapies

All concomitant medications taken during the study will be recorded in the eCRF. Complete information must be recorded on the concomitant medication page.

Once the subject receives the first dose of belimumab on Day 0, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically required in response to improving or worsening conditions. More latitude will be permitted for background medication changes in this extension study as compared to the parent study. Prohibited medications as outlined in Section 5.3.2 and Section 5.3.3 will still apply.

5.3.2. Prohibited Medications and Non-Drug Therapies

Subjects who start prohibited medications or therapies at any time during the study must be withdrawn from treatment with belimumab and enter study follow-up. 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).
- Other biologics (e.g., rituximab, abatacept, interleukin-1 receptor antagonist [anakinra]).
- Intravenous immunoglobulin (IVIG).
- IV cyclophosphamide.
- Plasmapheresis, leukapheresis.

5.3.3. Live Vaccines

Live vaccines are not permitted in the study. Subjects who require a live vaccine during the study should have belimumab discontinued prior to receiving the live vaccine and will be withdrawn from the study.

5.4. Treatment after the End of the Study

The continuation protocol of open-label belimumab will continue until the subject withdraws from the trial, or the subject elects to participate in another belimumab continuation study for SLE, or intravenous 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.

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.

5.5. 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.

6. STUDY ASSESSMENTS AND PROCEDURES

Table 2 Time and Events Table (Year 1)

Study Visit	Wk 48 of BEL 113750/ On/before Day 168 of C1115[1]	Wk 0 (Wk 52 of BEL113750/Day 168 of C1115) +1 week[1]	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	EXIT[2]	16 wk FU ± 7d post infusion	6 month FU ± 7d post infusion
Study Day		Day 0	28 ±7d	56 ±7d	84 ±7d	112 ± 7d	140 ±7d	168 ±7d	196 ±7d	224 ±7d	252 ±7d	280 ±7d	308 ±7d	336 ±7d			
Written Informed Consent	X																
Inclusion/Exclusion Criteria		X*															
Efficacy Assessments																	
Disease Activity Scales: SELENA SLEDAI, SLE Flare Index, BILAG and PGA [3]		X						X						X	X		
SLICC/ACR Damage Index		X												X	X		
Safety Assessments																	
Symptom-driven Physical Exam		X						X						X	X	X	
Record Concurrent Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess/Record Adverse Events[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs [5, 11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Visit	Wk 48 of BEL 113750/ On/before Day 168 of C1115[1]	Wk 0 (Wk 52 of BEL113750/Day 168 of C1115) +1 week[1]	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	EXIT[2]	16 wk FU ± 7d post infusion	6 month FU ± 7d post infusion
Study Day		Day 0	28 ±7d	56 ±7d	84 ±7d	112 ± 7d	140 ±7d	168 ±7d	196 ±7d	224 ±7d	252 ±7d	280 ±7d	308 ±7d	336 ±7d			
Laboratory Assessments																	
Labs: Haematology & Modified Chem 20 (non fasting) [5]		X	X		X			X			X			X	X	X	
Urinalysis[5]		X	X		X			X			X			X	X	X	
Spot urine (protein to creatinine ratio)[5, 6]		X						X						X	X		
Urine Pregnancy Test [5,7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C3, C4, Anti-ds DNA Autoantibodies[5]		X						X						X	X		
IgG [5, 8]		X			X			X						X	X	X	
IgA & IgM [5, 8]		X												X	X		
PT/ PTT		X*															
Exploratory Lab Assessments																	
Immunogenicity [9]		X						X						X	X	X	X[9A]
B cell Markers[10]		X												X	X		X
Investigational Product																	
Belimumab Administration[11, 12]		X*	X	X	X	X	X	X	X	X	X	X	X	X			

Table 2 Time and Events Table (Continued)

Calendar represents a yearly (48-week) ongoing visit schedule until the subject is terminated from the study. During the first 48 weeks, the 1st visit is Baseline/Day 0. For all subsequent 48 week calendar years, the 1st visit will be Week 4.

*See footnote 1.

1. **For subjects from BEL113750**: The Week 52 visit in the parent study Protocol BEL113750 serves as the Day 0 visit for the Protocol BEL114333. Performance of all the Week 52 procedures in BEL113750 will cover nearly all the procedures that are required for Day 0 of this protocol. Procedures necessary for both this protocol and the prior Phase III protocol need only be performed once and shall be recorded to CRFs as described in Section 6.1. At Week 48 of BEL113750, a subject should sign the informed consent for the BEL114333 study. In addition to the Week 52 procedures for BEL113750, a subject should be reassessed for inclusion/exclusion criteria of the BEL114333 study and receive belimumab (those procedures marked with an asterisk). Subjects must be able to receive the 1st dose of belimumab (Day 0) for BEL114333 four weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750.
   For subjects from C1115: The Day 168 (Week 24) visit in the open-label extension phase of C1115 serves as the Day 0 visit for the Protocol BEL114333. Performance of all the Day 168 procedures in C1115 will cover nearly all the procedures that are required for Day 0 of this protocol. Procedures necessary for both this protocol and the prior Phase III protocol need only be performed once and shall be recorded to CRFs as described in Section 6.1. On or before the Day 168 visit, a subject should sign the informed consent for the BEL114333 study. In addition to the Day 168 procedures for C1115, a subject should be reassessed for inclusion/exclusion criteria of the BEL114333 study and receive IV belimumab. The target for starting IV belimumab (Day 0) for BEL114333 is 1 week after the last dose of SC belimumab (scheduled for Week 23 in the open-label extension). The EXIT visit of the C1115 study (Week 24) serves as the Day 0 visit for the Protocol BEL114333, and will have a +1 week visit window.
2. The Exit visit will occur approximately 4 weeks after the last dose of belimumab. Belimumab should not be administered, and all Exit visit assessments must be completed.
3. Refer to Section 6.2.2.3 for guidelines for scoring proteinuria for SELENA SLEDAI and BILAG evaluation.
4. AE reports should be updated or completed prior to dosing. Ongoing Adverse events of BEL113750 have to be transferred and followed up in BEL114333.
5. Samples should be obtained prior to dosing.
6. A 24-hour urine may be done as an additional assessment if clinically indicated (e.g., renal flare).
7. Results of urine pregnancy test at subsequent visits, if required, must be available prior to dose. See 'Critical Baseline Assessments', Section 6.1 for definition of those exempted from subsequent pregnancy testing.
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.
   [9A]For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.
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). Note: B-cell subsets to be drawn at selected sites only.
11. It is recommended the patient be weighed at each visit prior to dosing. If weight changes by more than 5% from the Day 0 weight, the weight at the current visit should be used for calculating the dose. Systolic and diastolic blood pressure (sitting), heart rate, and oral temperature will be measured (see Section 6.3.11).
12. Subjects will remain under clinical supervision for 3 hours after completion of the first 2 infusions. See Section 5 and Section 6.3.9.

Table 3 Time and Events Table (Additional Years)

Study Visit	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	EXIT[1]	16 wk FU ± 7d post infusion	6 month FU ± 7d post infusion
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, BILAG and PGA [2]						X						X	X		
SLICC/ACR Damage Index												X	X		
Safety Assessments															
Symptom-driven Physical Exam						X						X	X	X	
Record Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess/Record Adverse Events [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs [4, 10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments															
Labs: Haematology & Modified Chem 20 (non fasting) [4, 11]						X						X	X	X	
Urinalysis [5, 11]						X						X	X	X	
Spot urine (protein to creatinine ratio) [4, 5, 11]						X						X	X		
Urine Pregnancy Test [6, 11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C3, C4, Anti-dsDNA Autoantibodies[4, 11]						X						X	X		
IgG [4, 7, 11]												X	X	X	
IgA & IgM [4, 7, 11]												X	X		

Study Visit	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	EXIT[1]	16 wk FU ± 7d post infusion	6 month FU ± 7d post infusion
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			
Exploratory Lab Assessments															
Immunogenicity[8]						X						X	X	X	X[8A]
B cell Markers[9]												X	X		X
Investigational Product															
Belimumab Administration[10]	X	X	X	X	X	X	X	X	X	X	X	X			

Calendar represents a yearly (48-week) ongoing visit schedule until the subject is terminated from the study.

1. The Exit visit will occur approximately 4 weeks after the last dose of belimumab. Study agent should not be administered, and all Exit visit assessments must be completed.
2. Refer to Section 6.2.2.3 for guidelines for scoring proteinuria for SELENA SLEDAI and BILAG evaluation.
3. AE reports should be updated or completed prior to dosing. Ongoing Adverse events of BEL113750 or C1115 have to be transferred and followed up in BEL114333.
4. Samples should be obtained prior to dosing.
5. A 24-hour urine may be done as an additional assessment if clinically indicated (e.g., renal flare).
6. Results of urine pregnancy test at subsequent visits, if required, must be available prior to dose. See 'Critical Baseline Assessments', Section 6.1 for definition of those exempted from subsequent pregnancy testing.
7. Serum immunoglobulin isotypes: IgG, IgM, IgA.
8. Immunogenicity testing includes quantifying the amount of belimumab present in the samples using the belimumab PK assay.
   [8A]For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.
9. 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 subsets to be drawn at selected sites only.
10. It is recommended the patient be weighed at each visit prior to dosing. If weight changes by more than 5% from the Day 0 weight, the weight at the current visit should be used for calculating the dose. Systolic and diastolic blood pressure (sitting), heart rate, and oral temperature will be measured (see Section 6.3.11).
11. During "Additional years", investigators can obtain any of the same laboratory assessments that are mentioned for Year 1 (hematology, 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.

6.1. Critical Baseline Assessments

For subjects in BEL113750: Subjects will be assessed for eligibility at the Week 48 visit of BEL113750. Only subjects who complete BEL113750 through the Week 48 visit and have a final BEL113750 disease assessment at Week 52 are eligible for this study. Written informed consent (including consent for the use and disclosure of research-related health information) must be obtained. Subjects must be able to receive the first dose of belimumab for BEL114333 four weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750.

For subjects in C1115: Subjects will be assessed for eligibility at the Day 168 visit of C1115. Only subjects who complete C1115 through the open-label extension phase and have a final disease assessment at Day 168 are eligible for this study. Written informed consent (including consent for the use and disclosure of research-related health information) must be obtained on or before the Day 168 visit. Subjects must be able to receive the first dose of IV belimumab (Day 0) for BEL114333 one week after the last SC dose in C1115. The EXIT visit of the C1115 study (Week 24) serves as the Day 0 visit for the Protocol BEL114333, and will have a +1 week visit window.

6.1.1. Procedures (Day 0)

6.1.1.1. Subjects in BEL113750

The Week 52 visit in BEL113750 will serve as the Day 0 visit for Protocol BEL114333. The subject must sign the informed consent for this protocol between the Week 48 and Week 52 visits of the BEL113750 study prior to any procedure in this protocol (that is not present in the BEL113750 protocol) being performed. On Day 0 of this study, a subject will be reassessed for Inclusion/Exclusion criteria of the BEL114333 study and receive belimumab, after completing the Week 52 procedures from the BEL113750 study. Site personnel will access the IVRS to enrol the subject in the study.

Procedures necessary for this protocol and for the prior Phase III protocol (BEL113750) need only be performed once. The results of any Day 0 procedure in this protocol which are also part of the BEL113750 protocol should be recorded on the BEL113750 eCRF. Only the additional procedures required for this protocol will be recorded in the BEL114333 protocol eCRF. The relevant Week 52 eCRF data will be transferred to the Day 0 BEL114333 eCRF.

The following assessments will be performed as part of the Week 52 assessment on BEL113750 and need only be performed once as described above.

- Urine for pregnancy testing- for all women with an intact uterus, unless exempted from pregnancy testing (i.e., of non-childbearing potential - women who had a hysterectomy, are post-menopausal which is defined as 1 year without menses, have both ovaries surgically removed or have current documented female sterilization procedure).
- Record of Concurrent Medications.

- Adverse Events.
- Physical exam
- Vital signs (Systolic and diastolic blood pressure (sitting), heart rate, and oral temperature will be measured. See Section 6.3.11).
- Blood samples for: (see Appendix 5– Laboratory Tests):
  - Haematology.
  - Modified Chem 20 (non-fasting). (CPK MUST be done for subjects with myositis in order to score SELENA SLEDAI/BILAG).
  - Serum Immunoglobulin isotypes (IgG, IgM, IgA).
  - Immunogenicity testing.
  - Biological markers (Complement C3 and C4)
  - Anti-dsDNA autoantibodies.
  - 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) at selected sites.
- Urine sample for:
  - Routine urinalysis.
  - Spot urine for macroscopic/microscopic/proteinuria assessments.
- Disease activity scales:
  - Physician's Global Assessment (PGA). (See Appendix 1).
  - SELENA SLEDAI (See Appendix 1; refer to Section 6.2.2.3 Guidelines for Scoring Proteinuria).
  - SLE Flare Index. (See Appendix 1).
  - BILAG. (See Appendix 2).
  - SLICC/ACR Damage Index (See Appendix 3).

The following additional procedures beyond those described above are required at Day 0 for Protocol BEL114333:

- Ensure Informed Consent Form has been signed.
- Confirm Eligibility.
- PT/PTT
- Administer belimumab.

6.1.1.2. Subjects in C1115

The Day 168 visit of the open-label extension of C1115 will serve as the Day 0 visit for Protocol BEL114333. The subject must sign the informed consent for this protocol on or before the Day 168 visit of the open-label extension of C1115 prior to any procedure in this protocol (that is not present in the C1115 protocol) being performed. On Day 0 of this study, a subject will be reassessed for Inclusion/Exclusion criteria of the BEL114333 study and receive IV belimumab, after completing the Day 168 procedures from the C1115 study. Site personnel will access the IVRS to enrol the subject in the study.

Procedures necessary for this protocol and for the prior Phase III protocol (C1115) need only be performed once. The results of any Day 0 procedure in this protocol which are also part of the C1115 protocol should be recorded on the C1115 eCRF. Only the additional procedures required for this protocol will be recorded in the BEL114333 protocol eCRF.

The following assessments will be performed as part of the Day 168 assessment on C1115 and need only be performed once as described above and entered into the C1115 eCRF only.

- Urine for pregnancy testing- for all women with an intact uterus, unless exempted from pregnancy testing (i.e., of non-childbearing potential - women who had a hysterectomy, are post-menopausal which is defined as 1 year without menses, have both ovaries surgically removed or have current documented female sterilization procedure).
- Record of Concurrent Medications.
- Adverse Events.
- Blood samples for: (see Appendix 5– Laboratory Tests):
  - Haematology.
  - Modified Chem 20 (non-fasting). (CPK MUST be done for subjects with myositis in order to score SELENA SLEDAI/BILAG).
  - PT/PTT
  - Serum Immunoglobulin isotypes (IgG, IgM, IgA).
  - Immunogenicity testing.
  - Biological markers (Complement C3 and C4)
  - Anti-dsDNA autoantibodies.
  - 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) at selected sites.
- Urine sample for:
  - Routine urinalysis.

- Spot urine for macroscopic/microscopic/proteinuria assessments.

- Disease activity scales:
  - Physician's Global Assessment (PGA). (See Appendix 1).
  - SELENA SLEDAI (See Appendix 1; refer to Section 6.2.2.3 Guidelines for Scoring Proteinuria).
  - SLE Flare Index. (See Appendix 1).
  - BILAG. (See Appendix 2).

The above Day 168 eCRF data will be transferred programmatically from the C1115 eCRF and merged with the datasets for BEL114333. This data will not be visible in the BEL114333 eCRF.

The following additional procedures beyond those described above are required at Day 0 for Protocol BEL114333:

- Ensure Informed Consent Form has been signed.
- Confirm Eligibility.
- Physical exam
- Vital signs (Systolic and diastolic blood pressure (sitting), heart rate, and oral temperature will be measured. See Section 6.3.11).
- SLICC/ACR Damage Index (See Appendix 3).
- Administer belimumab.

6.2. Efficacy

6.2.1. Efficacy Endpoints

6.2.1.1. Primary Endpoint

The primary efficacy endpoint is response rate at each scheduled visit when complete efficacy evaluations occur (e.g., Weeks 24 and 48 of Year 1 and Year 2, etc).

- A response is defined as:
  - ≥4 point reduction from baseline in SELENA SLEDAI score,

  AND

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

  AND

- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (i.e., Weeks 24 and 48 of Year 1 and Year 2, etc).

6.2.1.2. Secondary Endpoints

- Percent of subjects with ≥ 4 point reduction from baseline in SELENA SLEDAI score assessed every 24 weeks.
- Number of days of daily prednisone dose ≤ 7.5 mg/day and/or reduced by 25% from baseline over time.
- Time to first severe SLE Flare Index (SFI) flares assessed over time.

  NOTE: Baseline will be defined as study Day 0 of BEL113750 study or C1115 study as appropriate. Additionally, for the group of subjects who received placebo in BEL113750, a secondary analysis will be performed by defining the baseline as Day 0 of the current study the day placebo subjects in BEL113750 will have begun to receive belimumab treatment. (See Section 8.1)

6.2.1.3. Other Endpoints

Disease Activity:

- Duration of primary response assessed every 24 weeks.
- Change in Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index assessed every 24 weeks.
- Percent change in PGA assessed every 24 weeks.

Flares:

- For analysis, SLE Flares will be defined in 3 ways:

  - BILAG 1A/2B Flare: A new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline.

  - BILAG A Flare: A new BILAG A organ domain score compared with baseline.

  - 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).
- Time to first SFI flare assessed over time.
- Time to first 1A/2B BILAG flare assessed over time.
- Time to first BILAG A flare assessed over time.

Organ-specific Measures:

- Renal flare rate and time to first renal flare assessed over time.
  - 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
   a. >1 g if the baseline value was <0.2 g,
   b. >2 g if the baseline value was 0.2 to 1 g, or
   c. More than twice the value at baseline if the baseline value is >1 g.
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 hematuria (≥11 to 20 RBCs/ hpf) or a reproducible increase in hematuria by 2 grades compared with baseline, associated with >25% dysmorphic RBCs, glomerular in origin, exclusive of menses, accompanied by either an 0.8 g increase in 24-hour urinary protein levels (equivalent) or new RBC casts [Alarcón-Segovia, 2003] .

- Percent change in proteinuria by visit.

Prednisone:

- Percent change from baseline of prednisone dose at each scheduled visit.
- Percent of subjects whose average prednisone dose has been reduced to ≤ 7.5 mg/day from > 7.5 mg/day at baseline over time.

Details of the analysis of other supporting endpoints will be given in the Reporting and Analysis Plan (RAP).

6.2.2. SELENA SLEDAI

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

6.2.2.1. SELENA SLEDAI Score

The SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) 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 SELENA SLEDAI 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 SLEDAI. The maximum theoretical score for the

SELENA SLEDAI is 105 (all 24 descriptors present simultaneously) with 0 indicating inactive disease. 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, see Section 6.2.2.2), measurement of anti-dsDNA, C3, C4, haematology, and urinalysis, and for subjects with myositis, CPK. Guidelines for scoring proteinuria are provided in Section 6.2.2.3.

SELENA SLEDAI will be assessed at Day 0 and then every 24 weeks thereafter.

A copy of the index is provided in Appendix 1.

6.2.2.2. Laboratory Tests for SELENA SLEDAI and BILAG

It has been demonstrated that 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; Ruggenenti, 1998; K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease, 2002; Price, 2005]. Given this information, spot urine protein:creatinine ratio will be used for determining proteinuria in this study for both the SELENA SLEDAI and BILAG disease activity indices.

Measurement of creatinine clearance (CrCl)/glomerular filtration rate (GFR) using timed (for example, 24-hour) urine collections is time consuming and error prone and has consistently been shown to be no more, and often less, reliable than serum creatinine based equations for the estimation of GFR [K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease, 2002]. Therefore, GFR estimated by the Cockroft-Gault formula will be used in the BILAG disease activity index, as was done in the Phase II trial of belimumab (LBSL02) and Phase III.

Cockroft-Gault Equation [Cockcroft, 1976]

$$Cl_{cr}(mL/\min) = \frac{(140 - age(yrs))xweight(kg)}{72xserumcreatinine(mg/dL)}\ x\ 0.85\ if\ \ female$$

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

BILAG item # 75 for Creatinine (plasma/serum)

Sex	US (units)	UK (units)
Male and Female	0.5 – 1.4 mg/dL	44 – 124 µmol/l

BILAG item # 76 for Creatinine Clearance/GFR

Sex	US (units)
Male	85 – 125 ml/min
Female	75 – 115 ml/min

6.2.2.3. Guidelines for Scoring Proteinuria for SELENA SLEDAI

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

6.2.2.3.1. 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 prior to treatment. Two assessments of 24-hour proteinuria (by spot urine protein to creatinine ratio) obtained in a 2 to 3 week period are unlikely to show a > 0.5 g/24 hour equivalent increase except in acute renal flare. This is problematic for data analysis since the percent change in the disease activity scales are calculated from the baseline (not screening) SELENA SLEDAI score. As such, the following scoring rules will be applied:

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.

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.

6.2.2.4. SELENA SLEDAI 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.

6.2.2.5. Physician's Global Assessment (PGA)

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) designed for the physician to indicate the subject's overall disease activity at a particular visit [Petri, 1999]. It is part of the validated SELENA SLEDAI index. Either the primary investigator or a subinvestigator will score the PGA for the subject, and the same person will evaluate the subject each time, unless agreed with the GSK medical monitor. Each PGA measurement will be transformed linearly (x 3/10) to obtain a value between 0.00 and 3.00.

PGA will be assessed at Day 0 and then every 24 weeks thereafter.

A copy of the PGA VAS is provided in Appendix 1.

6.2.3. BILAG

The BILAG index is a clinical measure of lupus disease activity. The scoring system for the BILAG index was developed based upon the principle of the physician's intention to treat. The main distinguishing feature of the BILAG index from other disease activity indices is that disease activity in different organs/systems is reported separately. There are 8 organ systems: general, mucocutaneous, neurological, musculoskeletal, cardiorespiratory, vasculitis, renal, and hematological [Hay, 1993; Isenberg, 2000; Gordon, 2003]. A score is calculated for each system depending on the SLE clinical manifestations (or signs and symptoms) present and whether they are new, worse, the same, improving, or not present in the last 4 weeks compared with the previous 4 weeks. The SLE disease manifestations considered severe in each system are those that would normally require high dose steroids (prednisolone > 20 mg/day or equivalent) and/or cytotoxic agents; these define a BILAG A score. More moderate SLE disease manifestations that would be considered appropriate to treat with lower dose steroids, antimalarial drugs or NSAIDs contribute to a BILAG B score. Mild symptomatic SLE features that require only symptomatic therapy (e.g., analgesics and NSAIDs) contribute to a C score. If there are no current symptoms, but the system has previously been involved, then a D is recorded, while if the system has never been involved an E score is assigned.

The BILAG will be assessed at Day 0 and then every 24 weeks thereafter.

A copy of the BILAG index is provided in Appendix 2. All site staff scoring BILAG assessments are required to pass proficiency tests before carrying out assessments to ensure consistency across centres.

6.2.4. 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. In order for a feature to represent damage, it had to 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.

SLICC/ACR Damage Index will be assessed at Day 0 and the 48/Exit visit.

A copy of the SLICC/ACR Damage Index is provided in Appendix 3.

6.3. Safety

The safety assessments will be as follows:

- Adverse Event (including infusion-related and hypersensitivity reactions, infections and malignancies) reported throughout each 48 week period.
- Haematological and clinical chemistry parameters (including urinalysis) throughout each 48 week period and follow-up.
- B Cell Markers assessed at the Week 48 visit, EXIT visit, and at approximately 6 months after the last dose of study agent. Samples will be collected pre-dose where taken at dosing visits. Blood samples for measurement of B-cell subsets will be collected from subjects at selected sites only.
- Immunogenicity over each 24 week period, at the Exit visit and the 16 week follow-up visit for subjects who withdraw prior to completion of the 52-week treatment period. An attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent for any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available). Any anti-belimumab antibody positive sample will be tested for neutralization.
- Additional safety tests (such as vital signs, physical examinations and laboratory safety tests) or change in timing or addition of assessments may be performed during

the course of the study based on newly available data if recommended by the GSK internal Safety Review Team, to ensure appropriate safety monitoring. IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme.

- Note: The Columbia Suicide Severity Rating Scale (C-SSRS) will not be collected; however, investigators will continue to observe and clinically assess subjects for potential suicidality at all visits.

6.3.1. Liver Chemistry Stopping and Follow up Criteria

Refer to the diagram in Appendix 4 for a visual presentation of the procedures listed below.

NOTE: if serum bilirubin fractionation is not immediately available, belimumab should be discontinued if ALT ≥ 3xULN **and** bilirubin ≥ 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.

Phase III-IV liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance).

Phase III-IV liver chemistry stopping criteria 1-5 are defined below:

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

NOTE: if serum bilirubin fractionation is not immediately available, belimumab should be discontinued if ALT ≥ 3xULN and bilirubin ≥ 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 ≥ 8xULN.
3. ALT ≥ 5xULN but <8 x ULN persists for ≥2 weeks
4. ALT ≥ 3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
5. ALT ≥ 5xULN but <8 x ULN and cannot be monitored weekly for ≥2 weeks

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

- **Immediately** withdraw belimumab
- 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 ≥ 3xULN **and** bilirubin ≥ 2xULN (>35%

direct) (or ALT ≥ 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, belimumab should be discontinued if ALT ≥ 3xULN **and** bilirubin ≥ 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** (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
- Do not re-challenge with belimumab.

In addition, for 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

For 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.

Subjects with ALT ≥5xULN and <8xULN which exhibit a decrease to ALT x≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, 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, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

For 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
  - Hepatitis E IgM antibody
- 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 creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH)
- Fractionate bilirubin, if total bilirubin ≥2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of 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 ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease

6.3.2. 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.

6.3.2.1. 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 belimumab 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 belimumab or a concomitant medication (overdose per se will not be reported as an AE/SAE).

“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 fulfill 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

6.3.2.2. 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. Is medically important

   NOTE: 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.

6.3.3. 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.

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

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

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.

6.3.4. Investigator Evaluation of Adverse Events

The investigator will evaluate all adverse events with respect to seriousness (criteria for serious are listed in Section 6.3.2.2), 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), 2001 Adverse Event Severity Grade Tables (see Appendix 6), where possible:

SEVERITY:

Mild - An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities (Grade 1 DMID)

Moderate - An event that is sufficiently discomforting to interfere with 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.

6.3.5. Pregnancy

Any pregnancy that occurs during study participation and through 16 weeks following the last dose 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.

In the event that a subject becomes pregnant during the study, they should discontinue the study medication and be withdrawn from the study.

6.3.6. 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 study treatment (Week 0) and until the 16 week follow up visit.

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 6.3.7.

6.3.7. 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.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry abnormalities Phase III-IV:				
ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN **and** INR>1.5, if INR measured)***	24 hours*	SAE data collection tool. **Liver Event CRF and liver imaging and/or biopsy CRFs if applicable	24 hours	Updated SAE data collection tool. **Updated Liver Event CRF
ALT≥8xULN; ALT≥5xULN with hepatitis or rash or ≥3xULN and <5xULN that persists ≥4 weeks	24 hours*	**Liver event CRF	24 hours	**Updated Liver Event CRF
ALT≥5xULN plus bilirubin <2xULN	24 hours*	**Liver event CRF does not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks	24 hours	
ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks	24 hours*	**Liver event CRF	24 hours	Updated liver event CRF
ALT≥3xULN and <5x ULN and bilirubin <2xULN	24 hours*	**Liver event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks		

*GSK to be notified at onset of liver chemistry elevations to discuss subject safety.

** Liver event documents should be completed as soon as possible.

*** INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants

Criteria for liver chemistry stopping and follow up criteria can be found in Section 6.3.1.

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.

6.3.7.1. 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.

6.3.7.2. 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 6.3.6 .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

6.3.8. Laboratory Evaluations

Clinical laboratory tests will consist of a complete blood count (CBC) with differential, Chem-20, magnesium, and urinalysis (see list in Appendix 5). At the discretion of the Investigator, additional samples may be taken for safety reasons. Immunoglobulins, autoantibodies and serum complement (C3 and C4), will also be assessed (see Section 6.4). Samples (blood and urine) for clinical laboratory tests will be collected as described in the Time and Events schedule (Table 2 and Table 3).

All clinical laboratory blood samples will be sent to a central laboratory for analysis (details provided in the SPM). Standard reference ranges will be used. Full details of the collection and shipping requirements for the central laboratory are provided in the Central Laboratory Investigator Manual. The central laboratory will fax laboratory results to the Investigator and will transmit the results electronically to GlaxoSmithKline.

6.3.9. 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 should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

6.3.10. 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.

6.3.10.1. 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.

6.3.11. Vital Signs and Weight

Systolic and diastolic blood pressure (sitting), heart rate, and oral temperature will be measured. Measurements of vital signs and weight will be taken prior to dosing on Day 0 and every 4 weeks up to week 48/Exit; and at the 16-week follow-up visit (vital signs only) for subjects who withdraw prior to study completion. At the discretion of the Investigator, vital signs may be assessed at unscheduled visits.

6.3.12. Physical Examination

Abbreviated, symptom-driven examinations will be performed at Day 0, every 24 weeks, at the study Exit, and at the 16-week follow-up visit for subjects who withdraw. At the discretion of the Investigator, physical examinations may be performed at unscheduled visits.

As a minimum, brief physical examination will include assessment of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

6.3.13. Immunogenicity

6.3.13.1. Sample Collection and Handling

Serum samples will be collected for belimumab immunogenicity assays prior to dosing at Day 0, and Weeks 24 and 48 of Year 1 and Year 2, etc., and at the Exit visit, and 16 week follow-up visit. An attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent for any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available).

At each collection time, blood will be collected in a 6 mL plain tube. Each specimen will be allowed to clot, and the tube then centrifuged at approximately 1,600 g for 15 minutes at room temperature to separate the clot from the serum. The serum (approximately 1 mL per sample) will be harvested and placed in duplicate 2-mL Sarstedt vials for storage. Serum samples will be stored at -20°C at the sites before weekly batch shipment to Quest

Diagnostics. Samples will be stored at -70°C at Quest Diagnostics until shipment to HGS and stored at -80°C after they arrive at HGS. Samples will be shipped on dry ice in both shipments.

6.3.13.2. Assay Methods

Immunogenicity testing will be carried out at GSK (Clinical Immunology department) or Frontage Laboratories in Shanghai, China. The assay is performed in a 4-tiered belimumab immunogenicity assay paradigm (screening, confirmation/specificity and neutralisation and titer).

In the screening assay, the presence of anti-belimumab antibodies will be assessed using an electrochemiluminescence (ECL)-based (Meso Scale Discovery [MSD]) bridging assay after dissociation of belimumab from the anti-drug antibodies (ADA). Any samples testing positive will then be tested using a confirmatory ECL based assay which is able to distinguish between ADA (true positive) and BLyS-belimumab complexes in serum (false positive). The confirmed positive samples will be analyzed for the presence of neutralizing antibodies by a neutralisation assay and also assayed for titer. The results of the anti-belimumab antibody tests for all subjects will be reported at the end of the study.

6.4. Biomarker(s)

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.

Blood samples will be collected pre-dose at the visits specified in the Time and Events schedule (Table 2 and Table 3), to enable to following endpoints to be assessed:

- 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+/27BRIGHT/38BRIGHT SLE subset and CD20-/138+ plasma cells) at the Exit visit and 6 month Follow-up at selected sites.

All biomarker samples will be analysed centrally.

6.5. Pharmacokinetic Assessments

No PK sampling independent of immunogenicity testing, or liver chemistry stopping and follow-up criteria will be done. Immunogenicity samples will be tested for drug

levels using the belimumab PK assay to assist in the interpretation of the immunogenicity results.

7. DATA MANAGEMENT

For this study subject data will be entered into electronic case report forms (eCRFs), transmitted electronically to GSK or its partner company, HGS, 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. 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.

Data from C1115 Day 168 will be entered into the eCRF for C1115 and programmatically merged with the BEL114333 datasets. Any data cleaning procedures performed on this C1115 data will be completed in the C1115 eCRF before the final data transfer into BEL114333.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

There is no statistical sample size calculation. All analyses will be performed using descriptive statistics and will be exploratory in nature. The data base will be locked once all subjects have completed the Week 16 follow-up visit. Immunogenicity and B cell marker data collected at the 6-month post-treatment visit will be reported separately as an addendum to the clinical study report. Details of the analysis will be given in the Reporting and Analysis Plan (RAP).

8.1. Data Analysis Considerations

8.1.1. Primary Efficacy Analysis

The number and percent of subjects who respond at each scheduled visit when complete efficacy evaluations occur will be tabulated by treatment groups according to the treatment group that the subjects were assigned to during randomisation in BEL113750 study and the actual treatment they receive in the current study. The baseline will be defined as study Day 0 of BEL113750 study. Additionally, for the group of subjects who received placebo in BEL113750, a secondary analysis will be performed by defining the baseline as Day 0 of the current study the day placebo subjects in BEL113750 will have begun to receive belimumab treatment.

Subjects who previously received SC belimumab will be evaluated separately and this analysis will be described in the Reporting and Analysis Plan.

8.1.2. Analysis of Additional Efficacy and Biomarkers

For the primary analysis of the additional efficacy and biomarkers, the baseline will be defined as study Day 0 of BEL113750 Study. Additionally, for the group of subjects who received placebo in BEL113750 study, a secondary analysis will be performed by defining the baseline as the day placebo subjects in BEL113750 will have begun to receive belimumab treatment.

The major analysis of the additional efficacy and biomarkers will include the descriptive tabulation of secondary endpoints by treatment groups according to the treatment group that the subjects were assigned to during randomisation in BEL113750 study and the actual treatment they are assigned to in the current study.

Subjects who previously received SC belimumab will be evaluated separately and this analysis will be described in the Reporting and Analysis Plan.

8.1.3. Analysis of Safety Variables

AEs will be graded for severity by the investigator using Adverse Event Severity Grading Tables (Appendix 6) or the grades in Section 6.3.4, 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 during randomisation in the BEL113750 or C1115 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.

8.1.4. Interim Analysis

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.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov 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 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 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.

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 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 audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

9.5. Study and Site Closure

Subjects recruited into this study will continue to receive treatment with intravenous belimumab until such time as intravenous 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.

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 to the Clinical Trials Register 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.

The results summary will be posted to the Clinical Study Register at the time of the first regulatory approval or within 12 months of any decision to terminate development. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 12 months of the first approval or within 12 months of any decision to terminate development. 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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11. APPENDICES

11.1. Appendix 1: SELENA SLEDAI Disease Assessment Scales

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

SELENA SLEDAI Disease Assessment Scales (continued)

SLE Flare 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.

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.

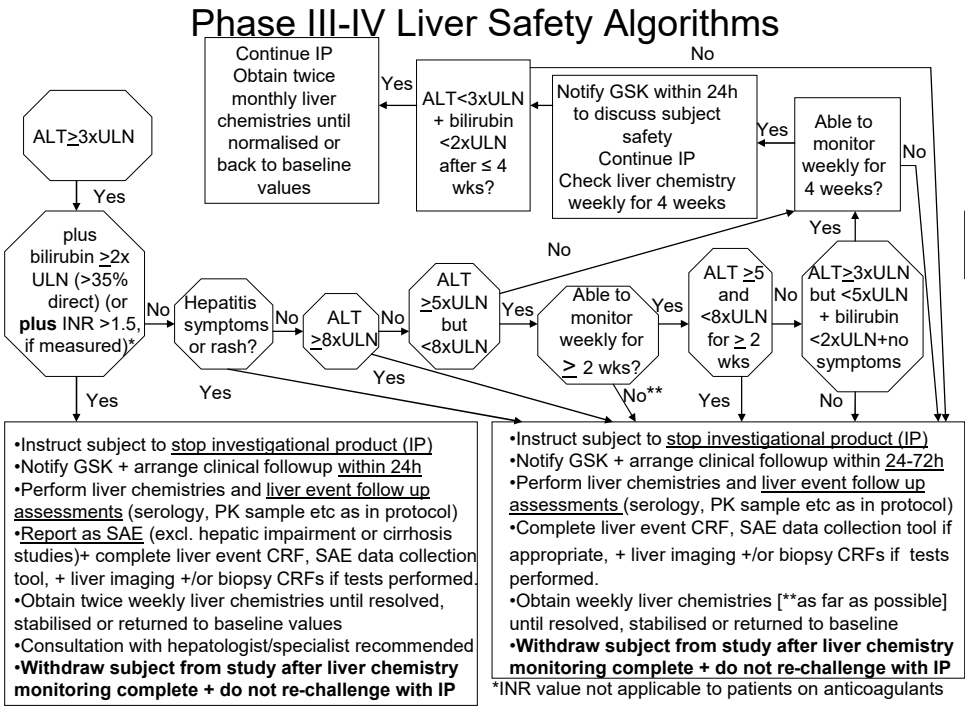
11.2. Appendix 2: BILAG Index Assessment

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.

11.3. Appendix 3: 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.

11.4. Appendix 4: Liver Chemistry Stopping and Followup Criteria



11.5. Appendix 5: Clinical Laboratory Tests

Hematology

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

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

Urinalysis

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

Spot Urine (protein : creatinine ratio)
Urine Pregnancy

Modified Chem-20

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

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

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

Biological Markers

Serum complement (C3 and C4)
B-cell subtypes

Immunoglobulins
Serum immunoglobulin isotypes: IgG, IgM, IgA

Immunogenicity

Autoantibodies
Anti-dsDNA

Liver event follow-up assessments:
- Hepatitis A IgM antibody
- HBsAg and hep B Core antibody (IgM)
- Hepatitis C RNA
- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody
- Hepatitis E IgM antibody
- CPK
- Anti-smooth muscle antibody
- Type 1 anti-liver kidney microsomal antibodies
- PK

11.6. Appendix 6: Adverse Event and Laboratory Value Severity Grade Tables

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

(continued)

*ULN = Upper Limit of Normal. Modified from DMID Adult Toxicity Tables, 2001

Appendix 6: Adverse Event and Laboratory Value Severity Grade Tables (continued)

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

(continued)

Modified from DMID Adult Toxicity Tables, 2001

Appendix 6: Adverse Event and Laboratory Value Severity Grade Tables (continued)

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

(continued)

Modified from DMID Adult Toxicity Tables, 2001

Appendix 6: Adverse Event and Laboratory Value Severity Grade Tables (continued)

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

(continued)

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

Modified from DMID Adult Toxicity Tables, 2001

Appendix 6: Adverse Event and Laboratory Value Severity Grade Tables (continued)

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

(continued)

Modified from DMID Adult Toxicity Tables, 2001

Appendix 6: Adverse Event and Laboratory Value Severity Grade Tables (continued)

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

URINALYSIS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proteinuria				
Dispstick Protein	1 +	2-3 +	4 +	Nephrotic syndrome
Spot Urine: Protein:Creatinine Ratio mg/mg	0.2-1.0	> 1.0-2.0	> 2.0-3.5	> 3.5
24 Hour Urine: Protein	200 mg - 1g loss/day	> 1-2 g loss/day	> 2-3.5 g loss/day	Nephrotic syndrome OR > 3.5 g loss/day
Hematuria	Microscopic only > 3 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 6: Adverse Event and Laboratory Value Severity Grade Tables (continued)

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

(continued)

Modified from DMID Adult Toxicity Tables, 2001

Appendix 6: Adverse Event and Laboratory Value Severity Grade Tables (continued)

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

(concluded)

Modified from DMID Adult Toxicity Tables, 2001

11.7. Appendix 7: Protocol Changes

Protocol Amendment 03

Protocol amendment 03 applies to sites in Japan.

Description of Changes

Changes are highlighted in bold.

Change 1: Title Page

This change affects the study title.

Change from:

BEL114333, a multicenter, continuation study of belimumab in subjects with systemic lupus erythematosus (SLE) who completed the phase III study BEL113750 in Northeast Asia

To:

BEL114333, a multicenter, continuation study of belimumab in subjects with systemic lupus erythematosus (SLE) who completed the phase III study BEL113750 in Northeast Asia **or completed the open-label extension of HGS1006-C1115 in Japan**

Rationale: Change made to add that the study will now include subjects who complete the open-label SC extension of C1115 in Japan.

Change 2: Protocol Summary, Rationale

This change affects Protocol Summary, Rationale, sentences 1 and 2.

Change from:

This study provides subjects who complete the BEL113750 Study in Northeast Asia the option of receiving belimumab, as an add-on to their standard of care (SOC) SLE therapy. All eligible subjects will receive belimumab 10 mg/kg irrespective of their randomized treatment in BEL113750.

To:

This study provides subjects who complete the BEL113750 Study in Northeast Asia **and subjects who complete the open-label extension of HGS1006-C1115 (referred to as C1115) Study in Japan** the option of receiving belimumab, as an add-on to their standard of care (SOC) SLE therapy. All eligible subjects will receive belimumab 10 mg/kg irrespective of their randomized treatment in BEL113750 **or C1115**.

Rationale: Changed made to add that subjects who complete the open-label SC extension of C1115 in Japan will have the option of continuing treatment with IV belimumab, as an add-on to their standard of care SLE therapy.

Change 3: Protocol Summary, Study Design

This change affects Protocol Summary, Study Design, paragraph 1.

Change from:

This is a multicentre, continuation study of belimumab plus SOC in SLE subjects who completed the Phase III BEL113750 protocol in Northeast Asia. Subjects participating in this protocol will continue to be monitored for safety and efficacy.

To:

This is a multicentre, continuation study of belimumab plus SOC in SLE subjects who completed the Phase III BEL113750 protocol in Northeast Asia **or who completed the open-label extension of the C1115 protocol in Japan**. Subjects participating in this protocol will continue to be monitored for safety and efficacy.

Rationale: Change made to add that subjects who complete the open-label SC extension of C1115 in Japan may be included in this study.

Change 4: Protocol Summary, Study Design

This change affects Protocol Summary, Study Design, paragraph 3.

Change from:

Subjects who complete 48 weeks of treatment on the BEL113750 and who meet inclusion/exclusion criteria, will be given the option to enter the continuation study. All subjects will receive belimumab 10 mg/kg IV infused over 1 hour every 28 days. The first dose on the continuation study must be given 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750.

To:

Subjects who complete 48 weeks of treatment on the BEL113750 **or complete the open-label extension of C1115** and who meet inclusion/exclusion criteria, will be given the option to enter the continuation study. All subjects will receive belimumab 10 mg/kg IV infused over 1 hour every 28 days. The first dose on the continuation study must be given 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750. **For subjects enrolling from C1115, the target for the first dose of IV belimumab is 1 week after the last dose of SC belimumab (scheduled for Week 23 in the open-label**

extension). The EXIT visit of the C1115 study (Week 24) serves as the Day 0 visit for the Protocol BEL114333, and will have a +1 week visit window.

Rationale: Change made to add that subjects who complete the open-label SC extension of C1115 in Japan may be included in this study and to provide timing of first dose of IV belimumab.

Change 5: Protocol Summary, Study Design

This change affects Protocol Summary, Study Design, paragraph 5.

Change from:

Prohibited medications in this study are similar to BEL113750.

To:

Prohibited medications in this study are similar to BEL113750 **and C1115**.

Rationale: Change made for clarification as subjects from more than one parent study will be enrolled.

Change 6: Protocol Summary, Study Design

This change affects Protocol Summary, Study Design, paragraph 6.

Change from:

Subjects recruited into this study will continue to receive treatment with belimumab until such time as belimumab becomes commercially available in a subject's country of participation, 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.

To:

Subjects recruited into this study will continue to receive treatment with **intravenous** belimumab until such time as **intravenous** belimumab becomes commercially available in a subject's country of participation, 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.

Rationale: Clarification for intravenous belimumab.

Change 7: Protocol Summary, Study Design

This change affects Protocol Summary, Study Design, paragraph 7.

Change from:

The maximum number of subjects enrolled in this study will not exceed the maximum number of subjects enrolled and randomized in Protocol BEL113750.

To:

The maximum number of subjects enrolled in this study will not exceed the maximum number of subjects enrolled and randomized in Protocol BEL113750 **plus the number of subjects from Japan from the open-label extension of the C1115 study**.

Rationale: Change made to add that number of subjects will include those who complete the open-label SC extension of C1115 in Japan.

Change 8: Protocol Summary, Study Design

This change affects Protocol Summary, Study Design, paragraph 8.

Change from:

A subject will be regarded as having completed the study if the subject is still participating in the study at the time belimumab becomes commercially available in a subject's country of participation, or upon the decision by the sponsor to discontinue the study.

To:

A subject will be regarded as having completed the study if the subject is still participating in the study at the time **intravenous** belimumab becomes commercially available in a subject's country of participation, or upon the decision by the sponsor to discontinue the study.

Rationale: Clarification for intravenous belimumab.

Change 9: Section 1.3 Clinical Experience with Belimumab

This change adds new sub-headings and a new sub-section on belimumab administered subcutaneously.

Added:

Section 1.3.1 Belimumab Administered Intravenously

Section 1.3.2 Belimumab Administered Subcutaneously

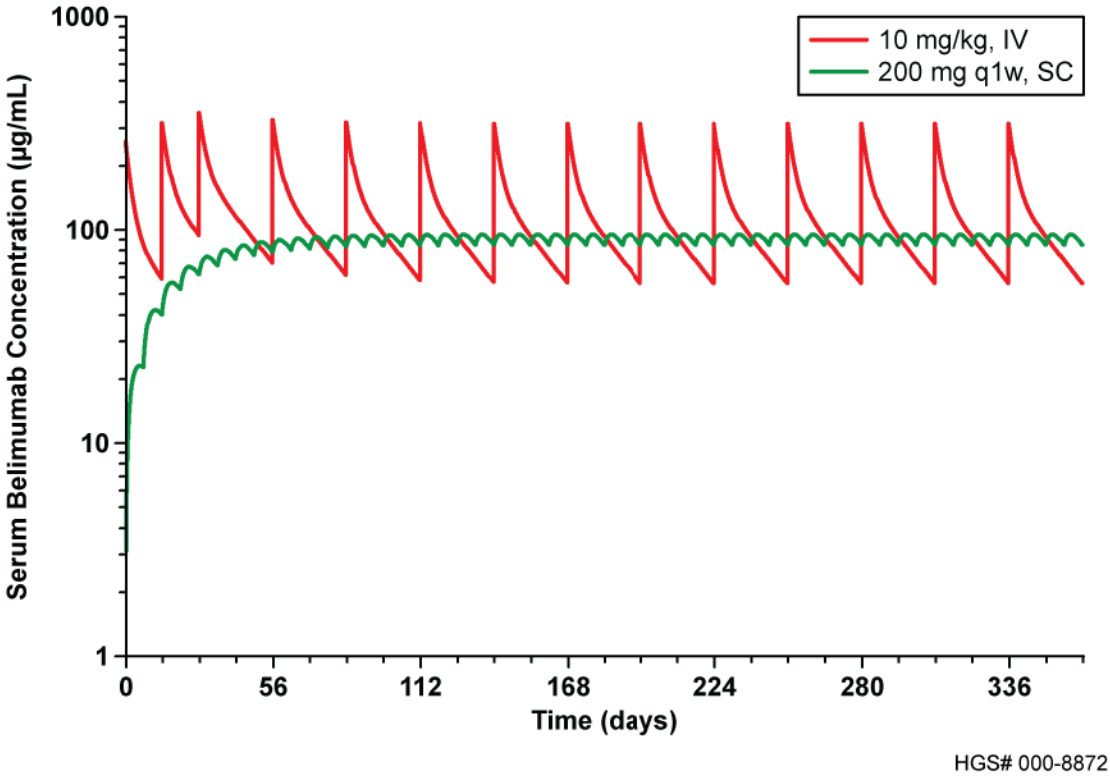
A subcutaneous (SC) liquid formulation of belimumab has been developed and is currently in a Phase 3 trial (Protocol HGS1006-C1115, referred to as C1115).

Based on PK data from the Phase 1 SC study (Protocol HGS1006-C1105, referred to as C1105), subjects given belimumab (200 mg/mL) 200 mg SC every week are expected to achieve on average similar steady-state AUC levels compared to those observed in the IV Phase 3 trials with 10 mg/kg IV every 4 weeks.

In the Phase 3 study, patients self-administer a fixed dose of 200 mg belimumab as an SC injection. Due to the relatively slow absorption from the subcutaneous to the central compartment, maximal serum belimumab concentrations following SC administration are not expected to exceed those observed following IV administration in the Phase 3 trials even for lower weight subjects (Figure 1).

Safety data for subcutaneous administration have been generated in a 24-week Phase 2 study using the original 100 mg/mL SC formulation in SLE patients (Protocol HGS1006-C1070, referred to as C1070). Although the number of subjects is small (N = 28), a dose of 300 mg weekly (100 mg SC 3x/wk) was generally well-tolerated (Study C1070, see Investigator's Brochure). In healthy Japanese male subjects, a single 200 mg SC dose vs a single IV dose of belimumab were evaluated in terms of safety and PK (BEL116119, see Investigator's Brochure). The bioavailability of the single SC dose of 200 mg belimumab in the subjects was estimated to be 77.5%. Geometric mean terminal half-life after single SC administration was 15.9 days which was comparable to the 17.7 days observed after single IV administration. All 7 AEs were mild or moderate in intensity. One event (cellulitis) reported in the IV group was judged to be related to the belimumab. No SAEs or AEs related to injection site reactions were reported during the study. [Shida, 2014]. Four weekly SC doses of belimumab at 2x120 or 200 mg were evaluated in healthy subjects in terms of safety and PK in Study C1105 and have been generally well tolerated.

Figure 1 Comparison of simulated mean belimumab serum concentration time profile with 10 mg/kg IV on days 0, 14, and 28 and Q4 weeks thereafter with simulated profile of 200 mg weekly SC



10 mg/kg IV data simulated using PK parameters from population PK analysis in SLE patients (HGS1006-POPPK); SC profile simulated using PK parameters from Study C1105 in healthy subjects.

The ongoing Phase 3 trial of SC belimumab in SLE patients (C1115) has completed enrollment with 839 patients as of 10 February 2014. The independent Data and Monitoring Committee reviews data from this study every 6 months; the most recent review was 29 October 2013 and no changes were recommended.

Rationale: Section added to provide background information regarding belimumab administered subcutaneously.

Change 10: Section 1.4, Rationale

This change affects Rationale, paragraph 1.

Change from:

This study provides subjects who complete the BEL113750 Study in Northeast Asia the option of receiving belimumab, as an add-on to their standard of care (SOC) SLE therapy. All eligible subjects will receive belimumab 10 mg/kg irrespective of their randomized treatment in BEL113750.

To:

This study provides subjects who complete the BEL113750 Study in Northeast Asia **or subjects from Japan who complete the open-label extension of C1115** the option of receiving belimumab, as an add-on to their standard of care (SOC) SLE therapy. All eligible subjects will receive belimumab 10 mg/kg irrespective of their randomized treatment in BEL113750 **or C1115**.

Rationale: Changed made to add that subjects who complete the open-label SC extension of C1115 in Japan will have the option of continuing treatment with IV belimumab, as an add-on to their standard of care SLE therapy.

Change 11: Section 3.1, Study Design

This change affects Study Design, paragraph 1.

Change from:

This is a multicentre, continuation study of belimumab plus SOC in SLE subjects who completed the Phase III BEL113750 protocol in Northeast Asia. Subjects participating in this protocol will continue to be monitored for safety and efficacy. The frequency of safety laboratory evaluations has been reduced in this protocol compared with BEL113750 based on the safety profile of belimumab studies to date and is not anticipated to compromise the well being and safety of subjects.

To:

This is a multicentre, continuation study of belimumab plus SOC in SLE subjects who completed the Phase III BEL113750 protocol in Northeast Asia **and subjects who completed the open-label extension of C1115 in Japan**. Subjects participating in this protocol will continue to be monitored for safety and efficacy. The frequency of safety laboratory evaluations has been reduced in this protocol compared with **the respective parent protocol** based on the safety profile of belimumab studies to date and is not anticipated to compromise the well being and safety of subjects.

Rationale: Changes made to add that subjects who complete the open-label SC extension of C1115 in Japan may be included in this study. Change made for clarification as subjects from more than one parent study will be enrolled.

Change 12: Section 3.1, Study Design

This change affects Study Design, paragraph 3.

Change from:

Subjects who complete 48 weeks of treatment on the BEL113750 study and who meet inclusion/exclusion criteria, and provide informed consent, will be given the option to enter the continuation study. All subjects will receive belimumab 10 mg/kg IV infused over 1 hour every 28 days. The first dose on the continuation study must be given 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750.

To:

Subjects who complete 48 weeks of treatment on the BEL113750 study **or complete the open-label extension of C1115** and who meet inclusion/exclusion criteria, and provide informed consent, will be given the option to enter the continuation study. All subjects will receive belimumab 10 mg/kg IV infused over 1 hour every 28 days. The first dose on the continuation study must be given 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750. **For subjects enrolling from C1115, the target for the first dose of IV belimumab is 1 week after the last dose of SC belimumab (scheduled for Week 23 in the open-label extension). The EXIT visit of the C1115 study (Week 24) serves as the Day 0 visit for the Protocol BEL114333, and will have a +1 week visit window.**

Rationale: Change made to add that subjects who complete the open-label SC extension of C1115 in Japan may be included in this study and to provide timing of first dose of IV belimumab.

Change 13: Section 3.1, Study Design

This change affects Study Design, paragraph 5.

Change from:

Subjects recruited into this study will continue to receive treatment with belimumab until such time as belimumab becomes commercially available in a subject's country of participation, 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.

To:

Subjects recruited into this study will continue to receive treatment with **intravenous** belimumab until such time as **intravenous** belimumab becomes commercially available in a subject's country of participation, 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.

Rationale: Clarification for intravenous belimumab.

Change 14: Section 3.1, Study Design

This change affects Study Design, last paragraph.

Change from:

A subject will be regarded as having completed the study if the subject is still participating in the study at the time belimumab becomes commercially available in a subject's country of participation, or upon the decision by the sponsor to discontinue the study.

To:

A subject will be regarded as having completed the study if the subject is still participating in the study at the time **intravenous** belimumab becomes commercially available in a subject's country of participation, or upon the decision by the sponsor to discontinue the study.

Rationale: Clarification for intravenous belimumab.

Change 15: Section 3.2 Discussion of Design

This change affects Discussion of Design, end of first paragraph.

Change from:

Subjects who completed 48 weeks of treatment and return for the final 52-week evaluation on BEL113750 may be recruited into this continuation protocol of open-label belimumab, which will continue until the subject withdraws from the trial, or belimumab becomes commercially available in the relevant participating country, or the subject elects to participate in another belimumab continuation study for SLE, or upon the decision by the sponsor to discontinue development/marketing of belimumab for SLE

To:

Subjects who completed 48 weeks of treatment and return for the final 52-week evaluation on BEL113750 may be recruited into this continuation protocol of open-label belimumab**. BEL114333 provides subjects who complete the open-label SC extension of C1115 in Japan the option of continuing treatment with IV belimumab, as an add-on to their standard of care SLE therapy.**

This study will continue until the subject withdraws from the trial, or **intravenous** belimumab becomes commercially available in the relevant participating country, or the

subject elects to participate in another belimumab continuation study for SLE, or upon the decision by the sponsor to discontinue development/marketing of belimumab for SLE

Rationale: Change made to add that the study will now include subjects who complete the open-label SC extension of C1115 in Japan.

Change 16: Section 4.1 Number of Subjects

This change affects the Number of Subjects.

Change from:

The maximum number of subjects enrolled in this study will not exceed the maximum number of subjects enrolled and randomized in Protocol BEL113750 in Northeast Asia.

To:

The maximum number of subjects enrolled in this study will not exceed the maximum number of subjects enrolled and randomized in Protocol BEL113750 in Northeast Asia **plus the number of subjects from Japan in the open label extension of the C1115 study**.

Rationale: Change made to add that number of subjects will include those who complete the open-label SC extension of C1115 in Japan.

Change 17: Section 4.2 Inclusion Criteria

This change affects Inclusion Criteria 1 and 2.

Change from:

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Have completed the BEL113750 Protocol in Northeast Asia through Week 48.

2. Be able to receive the first dose of belimumab for BEL114333 four weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750.

To:

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Have completed the BEL113750 Protocol in Northeast Asia through Week 48 **OR have completed the open-label extension of C1115 in Japan.**

2. Be able to receive the first dose of belimumab for BEL114333 four weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750 **OR be able to**

receive the first dose of IV belimumab 1 week (plus a 1 week visit window) after the last dose of open-label SC belimumab in C111**5**.

Rationale: Changes made to allow subjects who complete the open-label SC extension of C1115 in Japan to be included in this study and to provide timing of first dose of IV belimumab.

Change 18: Section 4.3 Exclusion Criteria

This change affects exclusion criteria 1.

Change from:

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 Phase 3 study that could, in the opinion of the principal investigator, put the subject at undue risk.

To:

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 **respective** Phase 3 stud**ies** that could, in the opinion of the principal investigator, put the subject at undue risk.

Rationale: Change made for clarification as subjects from more than one parent study will be enrolled.

Change 19: Section 5, Study Treatments

This change affects study treatment, paragraph 10

Change from:

The first dose on the continuation trial must be given 4 weeks (minimum 2 weeks, maximum 8 weeks) after the last dose in BEL113750. All subjects will receive belimumab 10 mg/kg IV infused over 1 hour every 28 days.

To:

The first dose on the continuation trial must be given 4 weeks (minimum 2 weeks, maximum 8 weeks) after the last dose in BEL113750. **For subjects enrolling from C1115, the target for the first dose of IV belimumab is 1 week after the last dose of SC belimumab (scheduled for Week 23 in the open-label extension). The EXIT visit**

of the C1115 study (Week 24) serves as the Day 0 visit for the Protocol BEL114333, and will have a +1 week visit window. All subjects will receive belimumab 10 mg/kg IV infused over 1 hour every 28 days.

Rationale: Changes made to provide timing of first dose of IV belimumab for subjects who enrol from the open-label SC extension of C1115 in Northeast Asia (Japan).

Change 20: Section 5.4, Treatment after the End of the Study

This change affects Treatment after the End of the Study, paragraph 1.

Change from:

The continuation protocol of open-label belimumab will continue until the subject withdraws from the trial, or the subject elects to participate in another belimumab continuation study for SLE, or 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.

To:

The continuation protocol of open-label belimumab will continue until the subject withdraws from the trial, or the subject elects to participate in another belimumab continuation study for SLE, or **intravenous 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.

Rationale: Clarification for intravenous belimumab.

Change 21: Section 6, Study Assessments and Procedures

This change affects Table 2, Column heading for Column 1 and 2.

Change from:

Column 1: Wk 48 of BEL 113750[1]

Column 2: Wk 0 (Wk 52 of BEL113750)[1]

To:

Column 1: Wk 48 of BEL 113750/**On/before Day 168 of C1115**[1]

Column 2: Wk 0 (Wk 52 of BEL113750/**Day 168 of C1115**)**+1 week**[1]

Rationale: Clarification of timing of visits for subjects enrolling from the open-label SC extension of C1115 in Northeast Asia (Japan)

Change 22: Section 6, Study Assessments and Procedures

This change affects Table 2, footnote 1.

Change from:

1. The Week 52 visit in the parent study Protocol BEL113750 serves as the Day 0 visit for the Protocol BEL114333. Performance of all the Week 52 procedures in BEL113750 will cover nearly all the procedures that are required for Day 0 of this protocol. Procedures necessary for both this protocol and the prior Phase III protocol need only be performed once and shall be recorded to CRFs as described in Section 6.1. At Week 48 of BEL113750, a subject should sign the informed consent for the BEL114333 study. In addition to the Week 52 procedures for BEL113750, a subject should be reassessed for inclusion/exclusion criteria of the BEL114333 study and receive belimumab (those procedures marked with an asterisk). Subjects must be able to receive the 1st dose of belimumab (Day 0) for BEL114333 four weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750.

To:

1. **For subjects from BEL113750:** The Week 52 visit in the parent study Protocol BEL113750 serves as the Day 0 visit for the Protocol BEL114333. Performance of all the Week 52 procedures in BEL113750 will cover nearly all the procedures that are required for Day 0 of this protocol. Procedures necessary for both this protocol and the prior Phase III protocol need only be performed once and shall be recorded to CRFs as described in Section 6.1. At Week 48 of BEL113750, a subject should sign the informed consent for the BEL114333 study. In addition to the Week 52 procedures for BEL113750, a subject should be reassessed for inclusion/exclusion criteria of the BEL114333 study and receive belimumab (those procedures marked with an asterisk). Subjects must be able to receive the 1st dose of belimumab (Day 0) for BEL114333 four weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750.
   For subjects from C1115: The Day 168 (Week 24) visit in the open-label extension phase of C1115 serves as the Day 0 visit for the Protocol BEL114333. Performance of all the Day 168 procedures in C1115 will cover nearly all the procedures that are required for Day 0 of this protocol. Procedures necessary for both this protocol and the prior Phase III protocol need only be performed once and shall be recorded to CRFs as described in Section 6.1. On or before the Day 168 visit, a subject should sign the informed consent for the BEL114333 study. In addition to the Day 168 procedures for C1115, a subject should be reassessed for inclusion/exclusion criteria of the BEL114333 study and receive IV belimumab. The target for starting IV belimumab (Day 0) for BEL114333 is 1 week after the last dose of SC belimumab (scheduled for Week 23 in the open-label extension). The EXIT visit of the C1115 study (Week 24) serves as the Day 0 visit for the Protocol BEL114333, and will have a +1 week visit window.

Rationale: Clarification of timing of visits and procedures for subjects enrolling from the open-label SC extension of C1115 in Northeast Asia (Japan).

Change 23: Section 6, Study Assessments and Procedures

This change affects Table 3, footnote 3.

Change from:

3. AE reports should be updated or completed prior to dosing. Ongoing Adverse events of BEL113750 have to be transferred and followed up in BEL114333.

To:

3. AE reports should be updated or completed prior to dosing. Ongoing Adverse events of BEL113750 **or C1115** have to be transferred and followed up in BEL114333.

Rationale: Change made for clarification as subjects from more than one parent study will be enrolled.

Change 24: Section 6.1 Critical Baseline Assessments

This change affects Critical Baseline Assessments.

Change from:

Subjects will be assessed for eligibility at the Week 48 visit of BEL113750. Only subjects who complete BEL113750 through the Week 48 visit and have a final BEL113750 disease assessment at Week 52 are eligible for this study. Written informed consent (including consent for the use and disclosure of research-related health information) must be obtained. Subjects must be able to receive the first dose of belimumab for BEL114333 four weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750.

To:

For subjects in BEL113750: Subjects will be assessed for eligibility at the Week 48 visit of BEL113750. Only subjects who complete BEL113750 through the Week 48 visit and have a final BEL113750 disease assessment at Week 52 are eligible for this study. Written informed consent (including consent for the use and disclosure of research-related health information) must be obtained. Subjects must be able to receive the first dose of belimumab for BEL114333 four weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750.

For subjects in C1115: Subjects will be assessed for eligibility at the Day 168 visit of C1115. Only subjects who complete C1115 through the open-label extension phase and have a final disease assessment at Day 168 are eligible for this study. Written informed consent (including consent for the use and disclosure of research-related health information) must be obtained on or before the Day 168 visit. Subjects must be able to receive the first dose of IV belimumab (Day 0) for BEL114333 one week

after the last SC dose in C1115. The EXIT visit of the C1115 study (Week 24) serves as the Day 0 visit for the Protocol BEL114333, and will have a +1 week visit window.

Rationale: Change made for clarification as subjects from more than one parent study will be enrolled. Clarification of timing of visits and procedures for subjects enrolling from the open-label SC extension of C1115 in Japan.

Change 25: Section 6.1.1, Procedures (Day 0)

This change created a sub-section.

Added:

6.1.1.1 Subjects in BEL113750

Rationale: Change made for clarification as subjects from more than one parent study will be enrolled.

Change 26: Section 6.1.1, Procedures (Day 0)

This change added a new sub-section.

Added:

6.1.1.2 Subjects in C1115

The Day 168 visit of the open-label extension of C1115 will serve as the Day 0 visit for Protocol BEL114333. The subject must sign the informed consent for this protocol on or before the Day 168 visit of the open-label extension of C1115 prior to any procedure in this protocol (that is not present in the C1115 protocol) being performed. On Day 0 of this study, a subject will be reassessed for Inclusion/Exclusion criteria of the BEL114333 study and receive IV belimumab, after completing the Day 168 procedures from the C1115 study. Site personnel will access the IVRS to enrol the subject in the study.

Procedures necessary for this protocol and for the prior Phase III protocol (C1115) need only be performed once. The results of any Day 0 procedure in this protocol which are also part of the C1115 protocol should be recorded on the C1115 eCRF. Only the additional procedures required for this protocol will be recorded in the BEL114333 protocol eCRF.

The following assessments will be performed as part of the Day 168 assessment on C1115 and need only be performed once as described above and entered into the C1115 eCRF only.

- **Urine for pregnancy testing- for all women with an intact uterus, unless exempted from pregnancy testing (i.e., of non-childbearing potential - women who had a hysterectomy, are post-menopausal which is defined as 1 year without menses, have both ovaries surgically removed or have current documented female sterilization procedure).**
- **Record of Concurrent Medications.**
- **Adverse Events.**
- **Blood samples for: (see Appendix 5– Laboratory Tests):**
  - **Haematology.**
  - **Modified Chem 20 (non-fasting). (CPK MUST be done for subjects with myositis in order to score SELENA SLEDAI/BILAG).**
  - **PT/PTT**
  - **Serum Immunoglobulin isotypes (IgG, IgM, IgA).**
  - **Immunogenicity testing.**
  - **Biological markers (Complement C3 and C4)**
  - **Anti-dsDNA autoantibodies.**
  - **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) at selected sites.**
- **Urine sample for:**
  - **Routine urinalysis.**
  - **Spot urine for macroscopic/microscopic/proteinuria assessments.**
- **Disease activity scales:**
  - **Physician's Global Assessment (PGA). (See Appendix 1).**
  - **SELENA SLEDAI (See Appendix 1; refer to Section 6.2.2.3 Guidelines for Scoring Proteinuria).**
  - **SLE Flare Index. (See Appendix 1).**
  - **BILAG. (See Appendix 2).**

The above Day 168 eCRF data will be transferred programmatically from the C1115 eCRF and merged with the datasets for BEL114333. This data will not be visible in the BEL114333 eCRF.

The following additional procedures beyond those described above are required at Day 0 for Protocol BEL114333:

- **Ensure Informed Consent Form has been signed.**
- **Confirm Eligibility.**

- **Physical exam**
- **Vital signs (Systolic and diastolic blood pressure (sitting), heart rate, and oral temperature will be measured. See Section 6.3.11).**
- **SLICC/ACR Damage Index (See Appendix 3).**
- **Administer belimumab.**

Rationale: Clarification of procedures on Day 0 for subjects enrolling from the open-label SC extension of C1115 in Japan.

Change 27: Section 6.2.1.2, Secondary Endpoints

This change affects Secondary Endpoints, Note after 3rd bullet, first sentence.

Change from:

NOTE: Baseline will be defined as study Day 0 of BEL113750 study.

To:

NOTE: Baseline will be defined as study Day 0 of BEL113750 study **or C1115 study as appropriate**.

Rationale: Change made for clarification as subjects from more than one parent study will be enrolled.

Change 28: Section 6.3.10.1 Progressive Multifocal Leukoencephalopathy

This change affects Progressive multifocal leukoencephalopathy.

Change from:

There have been no reported cases of PML in subjects with SLE or RA treated with belimumab. However, patients with SLE may be at increased risk for PML secondary to SLE itself, as well as the concurrent use of immunosuppressive drugs. The most common signs and symptoms of PML include visual disturbances, ocular movements, ataxia, and mental status changes such as disorientation or confusion. Clinical signs and symptoms of PML and SLE can be similar. The investigator must exercise best judegment in further workup and clinical intervention as appropriate. If PML is suspected, this should 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 29: Section 6.3.13.2 Assay Methods

This change affects Immunogenicity, Assay Methods.

Change from:

~~All~~ immunogenicity testing will be carried out at ~~HGS (Rockville, Maryland). HGS has developed a 3-part~~ (screening, confirmation/specificity and neutralisation) belimumab immunogenicity assay paradigm.

In the screening assay, the presence of anti-belimumab antibodies will be assessed using an electrochemiluminescence (ECL)-based (Meso Scale Discovery [MSD]) bridging assay after dissociation of belimumab from the anti-drug antibodies (ADA). Any samples testing positive will then be tested using a confirmatory ECL based assay which is able to distinguish between ADA (true positive) and BLyS-belimumab complexes in serum (false positive). The confirmed positive samples will be analyzed for the presence of neutralizing antibodies by a neutralisation assay. The results of the anti-belimumab antibody tests for all subjects will be reported at the end of the study.

To:

Immunogenicity testing will be carried out at **GSK (Clinical Immunology department) or Frontage Laboratories in Shanghai, China**. **The assay is performed in a 4-tiered** belimumab immunogenicity assay paradigm (screening, confirmation/specificity and neutralisation **and titer**).

In the screening assay, the presence of anti-belimumab antibodies will be assessed using an electrochemiluminescence (ECL)-based (Meso Scale Discovery [MSD]) bridging assay after dissociation of belimumab from the anti-drug antibodies (ADA). Any samples testing positive will then be tested using a confirmatory ECL based assay which is able to distinguish between ADA (true positive) and BLyS-belimumab complexes in serum (false positive). The confirmed positive samples will be analyzed for the presence of neutralizing antibodies by a neutralisation assay **and also assayed for titer**. The results of the anti-belimumab antibody tests for all subjects will be reported at the end of the study.

Rationale: Modification to reflect current methods.

Change 30: Section 7 Data Management

This change was added to the end of the Data Management section.

Added:

Data from C1115 Day 168 will be entered into the eCRF for C1115 and programmatically merged with the BEL114333 datasets. Any data cleaning procedures performed on this C1115 data will be completed in the C1115 eCRF before the final data transfer into BEL114333.

Rationale: Clarification for how C1115 data will be handled.

Change 31: Section 8.1.1 Primary Efficacy Analysis

This change affects Primary Efficacy Analysis by adding a new sentence following the original text.

Added:

Subjects who previously received SC belimumab will be evaluated separately and this analysis will be described in the Reporting and Analysis Plan.

Rationale: Clarification regarding analysis of subjects enrolling from the open-label SC extension of C1115 in Japan.

Change 32: Section 8.1.2 Analysis of Additional Efficacy and Biomarkers

This change affects Analysis of Additional Efficacy and Biomarkers by adding a new sentence following the original text.

Added:

Subjects who previously received SC belimumab will be evaluated separately and this analysis will be described in the Reporting and Analysis Plan.

Rationale: Clarification regarding analysis of subjects enrolling from the open-label SC extension of C1115 in Japan.

Change 33: Section 8.1.3 Analysis of Safety Variables

This change affects Analysis of Safety Variables, paragraph 1, second sentence.

Change from:

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 during randomisation in the BEL113750 study.

To:

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 during randomisation in the BEL113750 **or C1115** study.

Rationale: Change made for clarification as subjects from more than one study will be in the analysis.

Change 34: Section 9.5 Study and Site Closure

This change affects Study and Site Closure, paragraph 1, first sentence.

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.

To:

Subjects recruited into this study will continue to receive treatment with **intravenous** belimumab until such time as **intravenous** 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.

Rationale: Clarification for intravenous belimumab.

Change 35: Section 10 References

The following reference was added to the list of references.

Shida, Y, Takahashi N, Sakamoto T, Ino H, Endo A, Hirama T. The pharmacokinetics and safety profiles of belimumab after single subcutaneous and intravenous doses in healthy Japanese volunteers. J Clin Pharm Ther 2014;39:97-101.

Protocol Amendment 02

Protocol amendment 02 applies to all countries and sites.

Description of Changes

Changes are highlighted in bold.

Change 1: Protocol Summary, Study Design

This change affects Protocol Summary, Study Design, end of 4th paragraph

Change from:

Clinical laboratory evaluations (haematology, chemistry and urinalysis), will occur 4 weeks (28 days), 12 weeks (84 days), 24 weeks (168 days), 36 weeks (252 days), and 48 weeks (336 days) after the first dose of study medication in this protocol, then every 24 weeks thereafter, and at the Exit visit and the Week 16 follow-up visit. Serum IgG will be evaluated at 12 weeks (84 days), 24 weeks (168 days) and 48 weeks (336 days) after the first dose of study medication and then every 48 weeks thereafter and at the Exit visit and the Week 16 follow-up visit. Serum IgA and IgM will be evaluated in this protocol at Week 0 and Week 48, and then every 48 weeks thereafter and at the Exit visit. Adverse events will be assessed at every visit except at the 6 month follow-up visit. Subjects should be clinically evaluated by their investigating physician at each visit. It is the investigator's responsibility to manage their patient's SLE as necessary. Complete efficacy evaluations (SELENA SLEDAI, BILAG, SLE Flare Index along with PGA) and evaluation of biomarkers will occur every 24 weeks (168 days).

To:

Clinical laboratory evaluations (haematology, chemistry and urinalysis), will occur 4 weeks (28 days), 12 weeks (84 days), 24 weeks (168 days), 36 weeks (252 days), and 48 weeks (336 days) after the first dose of study medication in this protocol, then every 24 weeks thereafter, and at the Exit visit and the Week 16 follow-up visit. Serum IgG will be evaluated at 12 weeks (84 days), 24 weeks (168 days) and 48 weeks (336 days) after the first dose of study medication and then every 48 weeks thereafter and at the Exit visit and the Week 16 follow-up visit. Serum IgA and IgM will be evaluated in this protocol at Week 0 and Week 48, and then every 48 weeks thereafter and at the Exit visit. Adverse events will be assessed at every visit except at the 6 month follow-up visit. Subjects should be clinically evaluated by their investigating physician at each visit. It is the investigator's responsibility to manage their patient's SLE as necessary. Complete efficacy evaluations (SELENA SLEDAI, BILAG, SLE Flare Index along with PGA) and evaluation of biomarkers will occur every 24 weeks (168 days). B-cell subsets will be collected at Week 48, the EXIT visit, and at approximately 6 months after the last dose of study agent, from subjects at selected sites only.

Rationale: Clarify that B-cell subsets will be collected only at selected sites instead of all subjects. Addition of B-cell subsets collected at Week 48 while subjects participate in the extension study will allow monitoring of B-cell subsets on a yearly basis.

Change 2: Protocol Summary, Study Design

This change affects Protocol Summary, Study Design, paragraph 5.

Change from:

During the course of the study, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate in response to improving or worsening conditions. Prohibited medications in this study are similar to BEL113750. Subjects who start prohibited medications or therapies (see Section 5.3.2 and Section 5.3.3) at any time during the study must be withdrawn from treatment with belimumab and enter study follow-up. After discontinuation of study medication, subjects will return for an Exit visit 4 weeks after the last study medication administration and for follow up visits at 16 weeks and 6 months after the last dose of study medication. Withdrawal of subjects from treatment and the procedures to be followed are described in Section 4.4

To:

During the course of the study, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate in response to improving or worsening conditions. Prohibited medications in this study are similar to BEL113750. Subjects who start prohibited medications or therapies (see Section 5.3.2 and Section 5.3.3) at any time during the study must be withdrawn from treatment with belimumab and enter study follow-up. After discontinuation of study medication, subjects will return for an Exit visit 4 weeks after the last study medication administration and for **a** follow up visit at 16 weeks ~~**and 6 months**~~ after the last dose of study medication**. For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.** Withdrawal of subjects from treatment and the procedures to be followed are described in Section 4.4.

Rationale: Subjects participating in this open-label extension study no longer need to remain blinded. Only subjects who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available) will have attempts made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.

Change 3: Protocol Summary, Study Endpoints/Assessments

This change affects Protocol Summary, Study Endpoints/Assessments, last paragraph

Change from:

All other endpoints will be derived from the following assessments: SELENA SLEDAI, PGA, BILAG, SLE Flare Index, prednisone dose, renal flare assessment, proteinuria,

biomarkers (immunoglobulins, complement, anti-dsDNA autoantibodies, and B cell subsets), immunogenicity, adverse events, clinical laboratory assessments (clinical chemistry and haematology) and plasma levels of belimumab.

To:

All other endpoints will be derived from the following assessments: SELENA SLEDAI, PGA, BILAG, SLE Flare Index, prednisone dose, renal flare assessment, proteinuria, biomarkers (immunoglobulins, complement, anti-dsDNA autoantibodies, and B cell subsets **(at selected sites)**), immunogenicity, adverse events, clinical laboratory assessments (clinical chemistry and haematology) and plasma levels of belimumab.

Rationale: Clarify that B-cell subsets will be collected only at selected sites instead of all subjects.

Change 4: Investigational Plan, Study Design

This change affects Section 3.1, Investigational Plan, Study Design, end of 3rd paragraph.

Change from:

Subjects who complete 48 weeks of treatment on the BEL113750 study and who meet inclusion/exclusion criteria, and provide informed consent, will be given the option to enter the continuation study. All subjects will receive belimumab 10 mg/kg IV infused over 1 hour every 28 days. The first dose on the continuation study must be given 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750. All subjects will continue therapies as prescribed by the investigator. During the course of the study, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate in response to improving or worsening conditions. However, subjects who start prohibited medications or therapies (see Section 5.3.2 and Section 5.3.3) at any time during the study must be withdrawn from treatment with belimumab and enter study follow-up. After discontinuation of belimumab, subjects will return for an Exit visit 4 weeks after the last study medication administration and for follow up visit at 16 weeks and 6 months after the last dose of belimumab. Withdrawal of subjects from treatment and the procedures to be followed are described in Section 4.4.

To:

Subjects who complete 48 weeks of treatment on the BEL113750 study and who meet inclusion/exclusion criteria, and provide informed consent, will be given the option to enter the continuation study. All subjects will receive belimumab 10 mg/kg IV infused over 1 hour every 28 days. The first dose on the continuation study must be given 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750. All subjects will continue therapies as prescribed by the investigator. During the course of the study, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate in response to improving or worsening conditions. However, subjects who start prohibited medications or therapies (see Section 5.3.2 and Section 5.3.3) at any time during the study must be withdrawn from treatment with belimumab and enter study follow-up. After discontinuation of belimumab, subjects will return for an Exit visit 4 weeks after the last study medication administration and for follow up visit at 16 weeks ~~**and 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 last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.** Withdrawal of subjects from treatment and the procedures to be followed are described in Section 4.4.

Rationale: Subjects participating in this open-label extension study no longer need to remain blinded. Only subjects who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available) will have attempts made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.

Change 5: Investigational Plan, Study Design

This change affects Section 3.1, Investigational Plan, Study Design, end of 4th paragraph

Change from:

Clinical laboratory evaluations (haematology, chemistry and urinalysis), will occur 4 weeks (28 days), 12 weeks (84 days), 24 weeks (168 days), 36 weeks (252 days), and 48 weeks (336 days) after the first dose of study medication on this protocol, then every 24 weeks thereafter and at the Exit visit and the Week 16 follow-up visit. Serum IgG will be evaluated at 12 weeks (84 days), 24 weeks (168 days) and 48 weeks (336 days) after the first dose of study medication and then every 48 weeks thereafter and at the Exit visit and the Week 16 follow-up visit. Adverse events will be assessed at every visit except at the 6 month follow-up visit. Subjects should be clinically evaluated by their investigating physician at each visit. It is the investigator's responsibility to manage their patient's SLE as necessary. Complete efficacy evaluations (SELENA SLEDAI, BILAG, SLE Flare Index along with PGA) and evaluation of biomarkers will occur every 24 weeks (168 days).

To:

Clinical laboratory evaluations (haematology, chemistry and urinalysis), will occur 4 weeks (28 days), 12 weeks (84 days), 24 weeks (168 days), 36 weeks (252 days), and 48 weeks (336 days) after the first dose of study medication on this protocol, then every 24 weeks thereafter and at the Exit visit and the Week 16 follow-up visit. Serum IgG will be evaluated at 12 weeks (84 days), 24 weeks (168 days) and 48 weeks (336 days) after the first dose of study medication and then every 48 weeks thereafter and at the Exit visit and the Week 16 follow-up visit. Adverse events will be assessed at every visit except at the 6 month follow-up visit. Subjects should be clinically evaluated by their investigating physician at each visit. It is the investigator's responsibility to manage their patient's SLE as necessary. Complete efficacy evaluations (SELENA SLEDAI, BILAG, SLE Flare Index along with PGA) and evaluation of biomarkers will occur every 24 weeks (168 days). **B-cell subsets will be collected at Week 48, the EXIT visit, and at approximately 6 months after the last dose of study agent, from subjects at selected sites only.**

Rationale: Clarify that B-cell subsets will be collected only at selected sites instead of all subjects. Addition of B-cell subsets collected at Week 48 while subjects participate in the extension study will allow monitoring of B-cell subsets at selected sites on a yearly basis.

Change 6: Withdrawal Criteria

This change affects Section 4.4, Withdrawal Criteria, first paragraph

Change from:

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue a subject from this study. Every effort should be made by the investigator to keep subjects in the study and to ensure return for the Exit visit 4 weeks after the last dose of belimumab, and the follow-up visits 16 weeks and 6 months after the last dose. Notwithstanding this requirement, the investigator should adjust concurrent medications as clinically required.

To:

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue a subject from this study. Every effort should be made by the investigator to keep subjects in the study and to ensure return for the Exit visit 4 weeks after the last dose of belimumab, and the follow-up visits 16 weeks ~~**and 6 months**~~ after the last dose. **For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent. From subjects at selected sites only, B-cell subsets will be collected at the EXIT visit and at approximately 6 months after the last dose of study agent.** Notwithstanding this requirement, the investigator should adjust concurrent medications as clinically required.

Rationale: Clarify that the 6 month visit post last dose will be for subjects who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available, and for B-cell subsets labs for subjects at selected sites).

Change 7: Study Treatments

This change affects Section 5, last paragraph

Change from:

If a subject experiences a clinically significant, potentially life-threatening (Grade 4) AE that in the clinical judgement of the investigator is possibly, probably or definitely related to belimumab then treatment with belimumab will be discontinued. The subject should be withdrawn from the study and followed at regularly scheduled monthly study visits as required until resolution of the AE(s) and must also return for follow-up at the Exit visit, 16 weeks, and 6 months after the last dose of belimumab.

To:

If a subject experiences a clinically significant, potentially life-threatening (Grade 4) AE that in the clinical judgement of the investigator is possibly, probably or definitely related to belimumab then treatment with belimumab will be discontinued. The subject should be withdrawn from the study and followed at regularly scheduled monthly study visits as required until resolution of the AE(s) and must also return for follow-up at the **EXIT visit 4 weeks after the last dose of belimumab, and the follow-up visit 16 weeks after the last dose. For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent. From subjects at selected sites only, B-cell subsets will be collected at the EXIT visit and at approximately 6 months after the last dose of study agent.**

Rationale: Clarify that the 6 month visit post last dose will be for subjects who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available, and for B-cell subsets labs for subjects at selected sites).

Change 8: Study Assessments and Procedures, Time and Events Table

This change affects Section 6, Time and Events Table, Table 2 (Year 1) and Table 3 (Additional Years), Exploratory Lab Assessments, B cell Markers

Add:

Add "**X**" at Week 48 to Time and Events Table exploratory lab assessment B cell marker row in both Table 2 (Year 1) and Table 3 (Additional Years)

Rationale: Addition of B-cell subsets collected at Week 48 while subjects participate in the extension study will allow monitoring of B-cell subsets at selected sites on a yearly basis.

Change 9: Study Assessments and Procedures

This change affects Section 6, Time and Events Table, Table 2 (Year 1), Exploratory Lab Assessment Immunogenicity row at 6 month follow-up visit column and Footnote 9

Change from:

"X" at 6 month follow-up visit column and Immunogenicity row

To:

"X[9A]"

And:

Footnote:

9. Immunogenicity testing includes quantifying the amount of belimumab present in the samples using the belimumab PK assay. For all subjects, a serum sample for anti-belimumab antibodies will be obtained at least 6 months after the last dose or upon completion of the study.

To:

9. Immunogenicity testing includes quantifying the amount of belimumab present in the samples using the belimumab PK assay. ~~**For all subjects, a serum sample for anti-belimumab antibodies will be obtained at least 6 months after the last dose or upon completion of the study.**~~

[9A]For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.

Rationale: Clarity is added to the Time and Events table with these changes. Subjects participating in this open-label extension study no longer need to remain blinded. Only subjects who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available) will have attempts made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.

Change 10: Study Assessments and Procedures

This change affects Section 6, Time and Events Table, Table 2 (Year 1), end of Footnote 10

Change from:

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).

To:

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 subsets to be drawn at selected sites only.**

Rationale: Clarify that B-cell subsets will be collected only at selected sites instead of all subjects.

Change 11: Study Assessments and Procedures

This change affects Section 6, Time and Events Table, Table 3 (Additional Years), Exploratory Lab Assessments Immunogenicity row and Footnote 8

Change from:

"X" at 6 month follow-up visit column and Immunogenicity row

To:

"X^{8A}"

And:

Footnote:

1. 8. Immunogenicity testing includes quantifying the amount of belimumab present in the samples using the belimumab PK assay. For all subjects, a serum sample for anti-belimumab antibodies will be obtained at least 6 months after the last dose or upon completion of the study.

To:

8. Immunogenicity testing includes quantifying the amount of belimumab present in the samples using the belimumab PK assay. ~~**For all subjects, a serum sample for anti-belimumab antibodies will be obtained at least 6 months after the last dose or upon completion of the study.**~~

[8A]For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.

Rationale: Clarity is added to the Time and Events table with these changes. Subjects participating in this open-label extension study no longer need to remain blinded. Only subjects who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available) will have attempts made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.

Change 12: Study Assessments and Procedures

This change affects Section 6, Time and Events Table, Table 3 (Additional Years), end of Footnote 9

Change from:

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).

To:

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 subsets to be drawn at selected sites only.**

Rationale: Clarify that B-cell subsets will be collected only at selected sites instead of all subjects.

Change 13: Procedures (Day 0)

This change affects Section 6.1.1, Procedures (Day 0), Blood Samples bullet, end of B-cell subsets sub-bullet

Change from:

- 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).

To:

- 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 selected sites.

  Rationale: Clarify that B-cell subsets will be collected only at selected sites instead of all subjects.

Change 14: Safety

This change affects Section 6.3, Safety, 3rd bullet point

Change from:

- B Cell Markers assessed at the EXIT visit and at approximately 6 months after the last dose of study agent. Samples will be collected pre-dose where taken at dosing visits. Blood samples for measurement of B-cell subsets will be collected from subjects at selected sites only.

To:

- B Cell Markers assessed at the Week 48 visit, EXIT visit, and at approximately 6 months after the last dose of study agent. Samples will be collected pre-dose where taken at dosing visits. Blood samples for measurement of B-cell subsets will be collected from subjects at selected sites only.

Rationale: Clarify that B-cell subsets will be collected only at selected sites instead of all subjects. Addition of B-cell subsets collected at Week 48 while subjects participate in the extension study will allow monitoring of B-cell subsets at selected sites on a yearly basis.

Change 15: Safety

This change affects Section 6.3, Safety, 4th bullet point

Change from:

- Immunogenicity over each 24 week period, at the Exit visit and the 16 week follow-up visit for subjects who withdraw prior to completion of the 52-week treatment period. A serum sample for anti-belimumab antibodies will be obtained approximately 6 months after the last dose of study agent. Any anti-belimumab antibody positive sample will be tested for neutralization.

To:

- Immunogenicity over each 24 week period, at the Exit visit and the 16 week follow-up visit for subjects who withdraw prior to completion of the 52-week treatment period. **An attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent for any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-**

up immunogenicity sample is not available). Any anti-belimumab antibody positive sample will be tested for neutralization.

Rationale: Subjects participating in this open-label extension study no longer need to remain blinded. Only subjects who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available) will have attempts made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.

Change 16: Sample Collection and Handling

This change affects Section 6.3.13.1, Sample Collection and Handling, first paragraph

Change from:

Serum samples will be collected for belimumab immunogenicity assays prior to dosing at Day 0, and Weeks 24 and 48 of Year 1 and Year 2, etc., and at the Exit visit, 16 week and 6 month follow-up visits.

To:

Serum samples will be collected for belimumab immunogenicity assays prior to dosing at Day 0, and Weeks 24 and 48 of Year 1 and Year 2, etc., and at the Exit visit, **and** 16 week **follow-up visit. ~~and 6 month follow-up visits.~~ An attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent for any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available).**

Rationale: Subjects participating in this open-label extension study no longer need to remain blinded. Only subjects who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available) will have attempts made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.

Change 17: Biomarkers

This change affects Section 6.4, end of last bullet point

Change from:

- 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 the Exit visit and 6 month Follow-up.

To:

- 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 the Exit visit and 6 month Follow-up **at selected sites.**

Rationale: Clarify that B-cell subsets will be collected only at selected sites instead of all subjects.

Protocol Amendment 01

Protocol amendment 01 applies to all countries and sites.

Description of Changes

Changes are highlighted in bold.

Change 1: Protocol Summary, Study Design

This change affects Protocol Summary, Study Design, paragraph 6.

Change from:

Subjects recruited into this study will continue to receive treatment with belimumab until such time as belimumab becomes commercially available in a subject's country of participation, 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.

To:

Subjects recruited into this study will continue to receive treatment with belimumab until such time as belimumab becomes commercially available in a subject's country of participation, **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.

Rationale: Sentence inadvertently omitted

Change 2: Inclusion Criteria

This change affects Section 4.2, Inclusion Criterion #3, after last bullet point

Add:

> 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).

Rationale: MMF can affect the metabolism and effectiveness of oral contraceptives. Based on this, it is recommended that women receiving MMF who rely on oral contraceptives for birth control should be required to use an additional method to minimize the risk of pregnancy.

Change 3: Study Treatments; Investigational Products and Reference Therapy

This change affects Section 5, paragraph 10, regarding new information on post-infusion observation time for potential hypersensitivity reactions for the first two infusions.

Change from:

Subjects will be monitored during and after each infusion according to study sites' guidelines or standard operating procedure for IV infusions. This may include, but is not limited to, monitoring vital signs and observing for any untoward reactions. Trained rescue personnel and rescue medications/equipment should be available for a minimum of the first dose.

To:

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. Otherwise, subjects will be monitored during and after each infusion according to study sites' guidelines or standard operating procedure for IV infusions. This may include, but is not limited to, monitoring vital signs and observing for any untoward reactions.

Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Trained rescue personnel and rescue medications/equipment should be available for a minimum of the first **2** doses.

Rationale: The protocol has been modified to require that subjects remain under clinical supervision for 3 hours after completion of the first 2 infusions. This change has been made to all upcoming trials of intravenous belimumab in adult subjects in order to provide a longer period of post infusion monitoring and to prospectively collect more precise data on hypersensitivity reactions. A broad review of spontaneous safety reports received as of January 2012 identified 18 serious hypersensitivity reactions for an estimated reporting rate of 0.4%. Of these events, all occurred with the 1st or 2nd infusion (where infusion number is known, n=15) and the vast majority occurred during or shortly after completion of the infusion. Five cases appear to have been delayed in onset beyond

1 hour after completion of the infusion (n=3) or recurred after initial resolution of initial early symptoms (n=2). Given the nature of postmarketing reporting, details surrounding these events are limited and precise information with respect to time of onset of initial symptoms relative to the infusion is not available. This clinical trial, as well as other upcoming clinical trials, provides an opportunity to better characterize the hypersensitivity reactions observed with belimumab, including signs and symptoms and time to onset. The protocol-defined minimum monitoring period is applied only to the first 2 infusions because it is with these infusions that the vast majority of hypersensitivity reactions have been observed. For all subsequent infusions, subjects should be monitored during and for an appropriate period of time after infusion according to site procedures/clinical judgment.

This will also maintain the blind in the parent study BEL113750.

Change 4: Withdrawal Criteria

This change affects Section 4.4: Withdrawal Criteria, second paragraph.

Remove:

"Sponsor request"

Rationale: The intention of "Sponsor request" was to clarify subject withdrawals in the case report forms due to the unlikely administrative event of study termination changes to the clinical development plan. The case report forms include "Study closed/Terminated" thus making "Sponsor request" redundant.

Change 5: Study Assessments and Procedures, Time and Events Table (Year 1)

This change affects Section 6: Study Assessments and Procedures, Table 2: Time and Events Table (Year 1 only), Investigational Product, addition of Footnote 12, regarding new information on post-infusion observation time for potential hypersensitivity reactions for the first two infusions.

Add:

Footnote 12: Subjects will remain under clinical supervision for three hours after completion of the first 2 infusions. See Section 5 and Section 6.3.9.

Rationale: The protocol has been modified to require that subjects remain under clinical supervision for 3 hours after completion of the first 2 infusions. This change has been made to all upcoming trials of intravenous belimumab in adult subjects in order to provide a longer period of post infusion monitoring and to prospectively collect more precise data on hypersensitivity reactions. A broad review of spontaneous safety reports received as of January 2012 identified 18 serious hypersensitivity reactions for an estimated reporting rate of 0.4%. Of these events, all occurred with the 1st or 2nd infusion (where infusion number is known, 15) and the vast majority occurred during or shortly after completion of the infusion. Five cases appear to have been delayed in onset beyond 1 hour after completion of the infusion (n=3) or recurred after initial resolution of initial

early symptoms (n=2). Given the nature of postmarketing reporting, details surrounding these events are limited and precise information with respect to time of onset of initial symptoms relative to the infusion is not available. This clinical trial, as well as other upcoming clinical trials, provides an opportunity to better characterize the hypersensitivity reactions observed with belimumab, including signs and symptoms and time to onset. The protocol-defined minimum monitoring period is applied only to the first 2 infusions because it is with these infusions that the vast majority of hypersensitivity reactions have been observed. For all subsequent infusions, subjects should be monitored during and for an appropriate period of time after infusion according to site procedures/clinical judgment.

This will also maintain the blind in the parent study BEL113750.

Change 6: Study Assessments and Procedures, Time and Events Table (Additional Years)

This change affects Section 6: Study Assessments and Procedures, Table 2: Time and Events Table (Additional Years), Laboratory Assessments, addition of Footnote 11.

Add:

Footnote 11: During "Additional Years", investigators can obtain any of the same laboratory assessments that are mentioned for Year 1 (hematology, 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.

Rationale: Clarification for investigators that labs are not limited to only every 6 months in "Additional Years" and investigators are able to obtain supplemental labs in addition to the scheduled every 6 month labs as in "Year 1" at the discretion of the investigator as unscheduled labs.

Change 7: Infusion-related Reactions and Hypersensitivity Reactions

This change affects Section 6.3.9: Infusion-reactions and Hypersensitivity Reactions, regarding new information on post-infusion observation time for potential hypersensitivity reactions for the first two infusions.

Add:

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. 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, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

Rationale: The protocol has been modified to require that subjects remain under clinical supervision for 3 hours after completion of the first 2 infusions. This change has been made to all upcoming trials of intravenous belimumab in adult subjects in order to

provide a longer period of post infusion monitoring and to prospectively collect more precise data on hypersensitivity reactions. A broad review of spontaneous safety reports received as of January 2012 identified 18 serious hypersensitivity reactions for an estimated reporting rate of 0.4%. Of these events, all occurred with the 1st or 2nd infusion (where infusion number is known, 15) and the vast majority occurred during or shortly after completion of the infusion. Five cases appear to have been delayed in onset beyond 1 hour after completion of the infusion (n=3) or recurred after initial resolution of initial early symptoms (n=2). Given the nature of postmarketing reporting, details surrounding these events are limited and precise information with respect to time of onset of initial symptoms relative to the infusion is not available. This clinical trial, as well as other upcoming clinical trials, provides an opportunity to better characterize the hypersensitivity reactions observed with belimumab, including signs and symptoms and time to onset. The protocol-defined minimum monitoring period is applied only to the first 2 infusions because it is with these infusions that the vast majority of hypersensitivity reactions have been observed. For all subsequent infusions, subjects should be monitored during and for an appropriate period of time after infusion according to site procedures/clinical judgment.

This will also maintain the blind in the parent study BEL113750.

Change 8: Appendix 5: Clinical Laboratory Tests

This change affects Section 11.5: Appendix 5: Clinical Laboratory Tests; Biological Marker: BLyS protein, and Autoantibody: aCL.

Remove:

BLyS protein and aCL

Rationale: These 2 laboratory tests are not obtained in this extension study