TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A single dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of GSK1550188 in Chinese subjects with Systemic Lupus Erythematosus (SLE)

Compound Number: GSK1550188

Development Phase: I

Effective Date: 15-MAR-2017

Protocol Amendment Number: 01

SYNOPSIS: GSK1550188 (belimumab, monoclonal anti-BLyS antibody) is a human $IgG_1\lambda$ monoclonal antibody that binds soluble BLyS with high affinity and inhibits its biological activity. Belimumab has been approved over 45 countries, including the United States (US), Canada, European Union, Switzerland, Brazil, and Australia for the treatment of adult patients with active autoantibody-positive SLE who are receiving standard therapy.

This is a single dose study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of 10 mg/kg GSK1550188 administered intravenously (IV) in Chinese subjects with Systemic Lupus Erythematosus (SLE).

Approximately 20 subjects will be enrolled to guarantee no less than 12 subjects complete dosing and critical assessments. After the study has been explained to the subjects and they have given full informed consent, the subjects will undergo a medical screen within 30 days prior to the first dose, to determine their eligibility for participation based on the inclusion/exclusion criteria.

After screening, eligible Chinese SLE subjects will be admitted to the study center on Day 0. Each subject will receive the dose on Day 0 after completion of all the pre-dose procedure. The subjects will be kept in the study center up to 24 hours post dosing with subsequent outpatient visits occurring on Days1, 7, 14, 21, 28, 42, 56, and 84.

Blood samples for PK and PD analysis will be taken at regular intervals after dosing. Safety will be assessed by adverse events, clinical laboratory evaluations and vital signs.

Subject: GSK1550188, belimumab, Systemic Lupus Erythematosus, safety and tolerability, pharmacokinetics, pharmacodynamics, Chinese subjects

Authors:

PPD	Clinical Pharmacology/ Modeling and Simulation
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	Statistics
	Data Management
	Clinical Operation

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2013N175219_00	2016-JAN-26	Original
2013N175219_01	2017-MAR-15	Amendment No. 1

Modification of Sponsor/medical monitor Information Page.

Modification of Table 1 to keep consistency with exclusion criteria and Section 6.2.1.1.

Changes to inclusion and exclusion criteria: Modification to inclusion criteria 4; Modification to exclusion criteria 7, 10, 14, and addition of exclusion criteria 21 and 22.

Modification of Section 4.2.3.1 to clarify contraceptive methods.

Clarification of text to Section 5.7.1.

Addition of prohibited drugs within 30 days prior to Day 0 in Section 5.7.2.

Changes to Section 6: Modification of paragraph 2; Modification of Table 2: Addition of inclusion/exclusion check at pre-dose on Day 0; Addition of footnote 2 and footnote 10. Modification of footnote 3. Addition of Table 3 to Section 6.

Addition of eligibility check at pre-dose on Day 0 to Section 6.1.2

Addition of additional IgG test required for subjects with ALT >3xULN AND Bilirubin >2xULN (>35% Direct Bilirubin) in Section 6.2.1.

Correct consistency errors.

SPONSOR SIGNATORY

PPD

15-03-2017

Date

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Chin

PPD

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

Medical Monitor and Sponsor Contact Information:

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 200909

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	anti-cardiolipin
ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
ALP	Alkaline phosphatase
ANA	Anti-nuclear antibody
anti-SM	anti-Smith antigen
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
BILAG	British Isles Lupus Assessment Group
BlyS	B lymphocyte Stimulator
BUN	Blood urea nitrogen
CI	Confidence Interval
CL	Systemic clearance of parent drug
Cmax	Maximum observed concentration
CNS	Central Nervous System
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRF	Case Report Form
CRP	C-reactive protein
CVA	Cerebrovascular accident
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic acid
dsDNA	double stranded DNA
EU	European Union
ECG	Electrocardiogram
EDC	Electronic data collection
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GSK	GlaxoSmithKline
Hb	Hemoglobin
Ht	Hematocrit
HBV	Hepatitis B virus
HbsAg	Hepatitis B surface antigen
HbcAb	Hepatitis B core antibody
HCVAb	Hepatitis C virus antibodies

HGS	Human Genome Sciences
HIV	Human Immunodeficiency Virus
h	Hour(s)
Ht	Hematocrit
HPLC	High-performance liquid chromatography
HR	Heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgA	Immunoglobulin A
IgM	Immunoglobulin M
IL	Interleukin
INN	International Non proprietary Name
INR	International normalised ratio
IP	Investigational product
IRB	Institutional Review Board
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IVIG	Intravenous immunoglobulin
kg	Kilogram
λz	Terminal phase rate constant
L	Liter
LDH	Lactate dehydrogenase
ln	Naperian (natural) logarithm
LOQ	Limit of quantification
LLQ	Lower limit of quantification
LSLV	Last Subject Last Visit
µg	Microgram
µL	Microliter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
Ml	Milliliter
MMF	Mycophenolate mofetil
msec	Milliseconds
NSAIDs	Non-steroidal anti-inflammatory drugs
O2	Oxygen
PD	Pharmacodynamic
PGA	Physician's Global Assessment
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PT	Prothrombin Time

PTT	Partial Thromboplastin Time
QC	Quality control
QTc	Corrected QT interval
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SELENA	Safety of Estrogen in Lupus National Assessment trial
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SOC	System Organ Class
SOP	Standard Operating Procedure
SPM	Study Procedures Manual
SRI	SLE responder index
SWFI	Sterile water for injection
T	Infusion duration
TACI	Transmembrane activator and calcium-modulator and cytophilin ligand interactor
TNF	Tumor necrosis factor
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
ULN	Upper limit of normal
UK	United Kingdom
US	United States
Vz	Volume of distribution
WBC	White blood cells

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1. INTRODUCTION

1.1. Brief Background

1.1.1. Systemic Lupus Erythematosus and clinical management of the disease

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 its 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 which produce pathogenic auto antibodies 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 over a 1 to 2 year period with several courses of high dose steroids and cyclophosphamide, there are trends of progressive relapsing 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 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 severe infections and certain carcinogenesis.

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]. SLE disease burden does not appear to be higher in China, when compared with US SLE prevalence estimates of 100.0/100,000 [Naleway, 2005; Chakravarty, 2007]. Conversely, SLE

prevalence in 5 regions (UK, Germany, France, Spain, and Italy) of European Union (EU) was estimated at 43.0/100,000 [Govoni, 2006; Lopez, 2003; Nightingale, 2006], which is lower than the estimation in China. In terms of disease activity, [Boers, 2006] reported more severe SLE among Asian patients admitted to a medical centre in Australia. 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.

1.1.2. GSK1550188 (Belimumab)

GSK1550188 (International Non proprietary Name [INN]: belimumab), developed by Human Genome Sciences (HGS), is a recombinant,-human, IgG1λ monoclonal antibody that binds to soluble B lymphocyte stimulator (BlyS) with high affinity and inhibits its biological activity. In the Phase 2 SLE (LBSL02) and Rheumatoid Arthritis (RA) (LBRA01) trials, belimumab reduced, but did not deplete, numbers of B lymphocyte subsets as well as auto antibodies. Overall, subjects with elevated levels of immunoglobulins at baseline experienced reductions in immunoglobulin levels or achieved normal levels. This observation supports the rationale that in patients with SLE, belimumab offers the potential to modulate B cells and specifically affect their activity by reducing BlyS-mediated signaling. This appears to occur in a disease-specific manner, as pathogenic auto antibodies are reduced. In LBRA01 rheumatoid factor (RF) and in LBSL02 anti-double stranded DNA (anti-dsDNA) both reduced approximately 30% with relative preservation of normal IgG levels. The lack of a general suppression of B cells across all subsets supports the hypothesis that belimumab modulates B cells and has the potential to preserve cells that respond to foreign or abnormal self antigens. A Phase 3, 52-week dose ranging study (HGS1006-C1057) of IV belimumab versus placebo was done in sero-positive SLE patients maintained on standard therapy. A significant reduction in an SLE Responder Index (SRI) combined response endpoint comprising Safety of Estrogen in Lupus National Assessment trial (SELENA) SLEDAI score, Physician's Global Assessment (PGA) score and British Isles Lupus Assessment Group (BILAG) organ assessment. This has been confirmed in a second longer term 76-week study (HGS1006-C1056) with the primary endpoint evaluated at Week 52.

Experience from open-label, long-term continuation trials of belimumab in SLE patients confirms prolonged treatment with belimumab is generally well tolerated. There is no apparent increase in the incidence rate of adverse events (AEs) or serious adverse events (SAEs) over time, including important events such as infections and malignancies. Long term belimumab treatment appears to provide sustained improvement in SLE disease activity and reduction of flares. The definitive assessment of the PK of belimumab is based on a population approach including data collected from subjects with SLE in the Phase 1 (LBSL01), Phase 2 (LBSL02), and Phase 3 (C1056 and C1057) studies. The PK of belimumab administered by IV infusion was well described by a linear 2-compartment model with clearance from the central compartment. After IV infusion, serum belimumab concentrations declined in a bi-exponential manner, with a distribution half-life of 1.1-1.8 days. The terminal half-life is 12.5 days for the 1 mg/kg dose and 19.4 days for the 10 mg/kg dose.

Further information is provided in the Investigator Brochure (IB) (Belimumab Investigator's Brochure).

1.2. Study Rationale

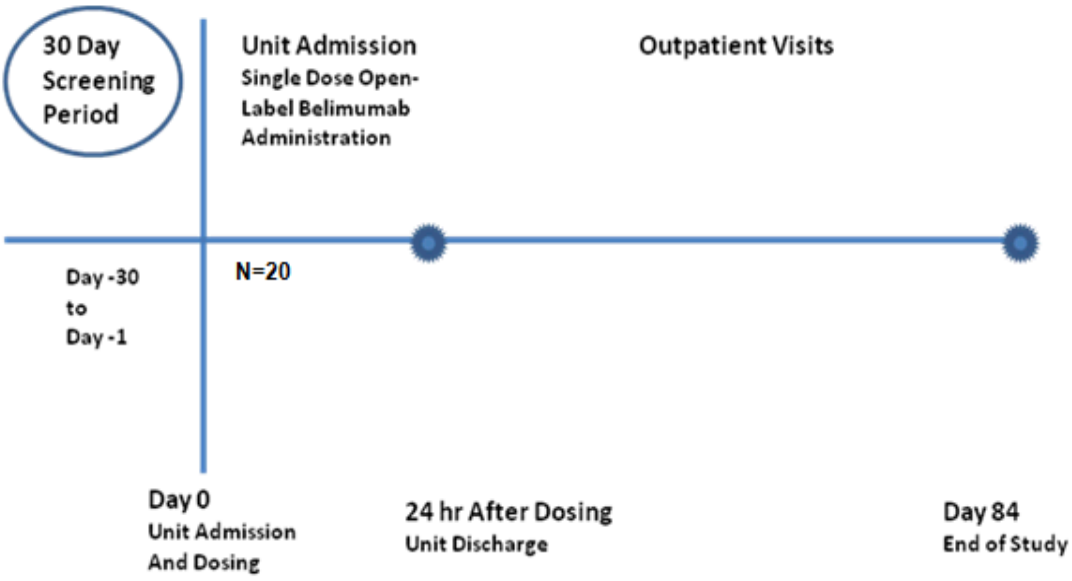
In China, GSK1550188 will be developed for a dosing regimen of once-monthly intravenous infusion for the treatment of SLE. The study described in this protocol will assess the safety, tolerability, pharmacokinetics and pharmacodynamics of single intravenous 10 mg/kg GSK1550188 in Chinese subjects with SLE and to support the registration of GSK1550188 in China.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To investigate the pharmacokinetics (PK) of intravenously (IV) administered GSK1550188 10 mg/kg in Chinese subjects with SLE.	Maximum observed concentration (Cmax), Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments (AUC [0-t]), Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time (AUC [0-∞]), Terminal phase half-life (t1/2), Terminal phase rate constant (λz), Systemic clearance of parent drug (CL), and Volume of distribution (Vz)
Secondary	
To evaluate the safety and tolerability of GSK1550188 in Chinese subjects with SLE. To investigate the effect of GSK1550188 on pharmacodynamics (PD) of B cell subsets	Safety and tolerability endpoints: adverse events, vital sign, 12-lead electrocardiogram (ECG), and clinical laboratory safety tests. 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).

3. STUDY DESIGN

3.1. Study Schematic



3.2. Study Design Detail

This will be a multicenter, single dose study of intravenous GSK1550188 at a dose of 10 mg/kg in Chinese subjects with SLE.

After the study has been explained to the subjects and they have given full informed consent, the subjects will undergo a medical screen within 30 days prior to the first dose, to determine their eligibility for participation based on the inclusion/exclusion criteria.

After screening, eligible Chinese SLE subjects will be admitted to the study center on Day 0. Each subject will receive the dose on Day 0 after completion of all the pre-dose procedure. The subjects will be kept in the study center up to 24 hours post dosing with subsequent outpatient visits occurring on Days1, 7, 14, 21, 28, 42, 56, and 84.

3.3. Discussion of Study Design

3.3.1. Design Rationale

This study is designed to assess the pharmacokinetics, safety, tolerability, and pharmacodynamics of a single intravenous 10mg/kg GSK1550188 dose in Chinese subjects with SLE. The study is open-label as the primary endpoint (pharmacokinetic parameters) will not be influenced by subjects knowing that they are receiving active treatment. The

subjects will have pharmacokinetic samples collected for 84 days (more than five half-lives) after dosing to enable a comprehensive pharmacokinetic profile to be generated. The pharmacokinetics of a single intravenous 10mg/kg GSK1550188 dose has never been assessed in healthy subjects, but has been assessed in Japanese (Study BEL114243) and Western subjects (Study LBSL01) with SLE. Therefore, Chinese subjects with SLE instead of Chinese healthy subjects will be recruited for this study to allow unbiased comparison between Chinese and non-Chinese subjects, if necessary.

3.3.2. Dose Rationale

The clinical studies of GSK1550188 in SLE subjects have shown GSK1550188 to be safe and well-tolerated when single doses of up to 20 mg/kg, or repeat doses at 1 mg/kg and 10 mg/kg for more than 76 weeks were administered. The 10 mg/kg GSK1550188 dose has been approved in the United States (US), Canada and European Union for the treatment of adult patients with active autoantibody-positive SLE who are receiving standard therapy. It is also the dose used in the on-going Phase III study BEL113750, which evaluates the efficacy and safety of 10 mg/kg belimumab in Northeast Asian (including China) subjects with SLE. Therefore, this study will use 10 mg/kg of GSK1550188 as the study dose.

3.4. Benefit-Risk Assessment

Belimumab administered by IV infusion is indicated for reducing disease activity in adult patients with active autoantibody positive SLE who are receiving standard therapy. The benefit/risk profile of belimumab for systemic lupus erythematosus remains favorable. Identified risks include hypersensitivity/infusion reactions and non-opportunistic infections. Potential risks (i.e., based on pharmacology but no association identified to date) include progressive multifocal leukoencephalopathy (PML) and other opportunistic infections; malignancies; immunogenicity; effects on immunizations (including interactions with live vaccine); and psychiatric events including depression and suicidality. The most common AEs reported in the primary safety population of adults with SLE were associated with hypersensitivity/infusion-related reactions, non-opportunistic infections, and symptoms consistent with SLE. The majority of reports of infusion-related and hypersensitivity reactions were non-serious and include symptoms such as nausea, vomiting, diarrhea, chills, fever, rash, urticaria, pruritus, headache, dizziness, and dyspnoea. However, infusion and hypersensitivity reactions can be severe and fatal. Most clinical trial and spontaneous cases of serious hypersensitivity occurred during or within the first hour after the completion of the infusion, although some cases report delayed acute onset (>4 hours but <4 days) or a delayed non-acute onset (4-21 days) hypersensitivity reactions.

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

belimumab and the risk of opportunistic infections, including PML, has been indentified to date, but data are limited. Progressive multifocal leukoencephalopathy resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. (See Table 1)

The primary data supporting efficacy of belimumab were the Phase 3 trials (C1056 and C1057) in which 1,684 subjects were treated for up to 52 weeks (C1057) or 76 weeks (C1056) (Belimumab IB, Section 5.3.1.2). Belimumab produced significant improvements in the SLE Responder Index as well as in individual component SELENA-SLEDAI score in both studies. Pooled analyses demonstrated steroid sparing, delay in median time to first flare, and decreased risk of severe flares over 52 weeks. Clinical trial data for belimumab since approval continue to show efficacy in the treatment of SLE through decreased SLE flares and decreased disease activity across multiple organ systems (Belimumab IB, Section 5.3.1.3). The safety profile of belimumab remains consistent with that known at approval and is consistent with expected events based on the mechanism of action and the disease under study.

In the post-marketing setting with IV belimumab, delayed onset of symptoms of acute hypersensitivity reactions as well as recurrence of clinically significant reactions after initial appropriate treatment has been observed. Belimumab should be administered by a healthcare professional prepared to treat hypersensitivity reactions including anaphylaxis. (See Table 1)

Table 1 Summary of key issues, their impact, and strategy to mitigate risk in this study.

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
Post-injection systemic reactions and Hypersensitivity	Administration of belimumab may result in infusion and hypersensitivity reactions, which can be severe and can be fatal. Non-serious infusion reactions and hypersensitivity reactions are common in SLE clinical trials with IV belimumab. Serious infusion and hypersensitivity reactions affected less than 1% of patients and included: anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnea. Delays in the onset of hypersensitivity reactions have been observed. Infusion reactions following administration of belimumab	Exclusion of subjects with a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.	Subjects should remain under clinical supervision for 3 hours after completion of the infusion. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing for any untoward reactions. Subjects should be made aware of the

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
	occurred more frequently on the first 2 infusion days and tended to decrease with subsequent administrations. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema.		potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Belimumab should be administered by a healthcare professional prepared to treat hypersensitivity reactions including anaphylaxis.
Infections	Infections occurred in a slightly greater proportion of subjects treated with belimumab compared with placebo. Infections occurring in at least 3% of patients receiving belimumab and at least 1% more frequently than patients receiving placebo were nasopharyngitis, bronchitis, pharyngitis, cystitis, and viral gastroenteritis. Serious infections occurred in 5% of patients receiving either belimumab or placebo.	Exclude patients with a history of any infection requiring hospitalization, antivirals or antibiotics within 4 weeks prior to Day 0., a history of or positive test at screening for HIV, Grade 3 or 4 lymphopenia, Grade 3 or 4 IgG or IgA deficiency. Patients should be excluded for serologic evidence of Hepatitis C (positive test) and evaluated for serologic evidence of Hepatitis B (HB) infection (HbsAg and anti-HbcAb). Patients with a positive HbsAg should be	Monitor patients for signs and symptoms of infection, monitor laboratory values, request that patients report signs of infection. Treat infections immediately and appropriately. If patient becomes hepatitis B core antibody positive and/or develop an ALT and/or AST >2.5 x ULN, obtain quantitative hepatitis B virus DNA. If the quantitative hepatitis B virus DNA result shows detectable viral loads, then the subject must be treated immediately and appropriately.

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
		excluded. Patients who are anti-HbcAb positive should be tested for HBV DNA. If DNA test is negative, the patient is eligible for inclusion	
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, consideration should be given to stopping immunosuppressant therapy. If PML is suspected, this should be immediately reported to the Medical Monitor.
Malignancies	As with other immunomodulating agents, the mechanism of action of belimumab may increase the potential risk for the development of malignancies.	Exclude patients with a history of malignant neoplasm within the last 5 years, except for adequately treated basal or squamous cell cancers of the skin, or carcinoma in situ	Monitor patients for signs and symptoms of malignancy, monitor laboratory values, request that patients report signs and symptoms. Treat appropriately.

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring
		of the uterine cervix.	
Effects on immunizations including reactions with live vaccines	No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving belimumab. Because of its mechanism of action, belimumab may interfere with the response to immunisations. The efficacy of concurrent vaccination in patients receiving belimumab is under investigation. Limited data suggest that belimumab does not significantly affect the ability to maintain a protective immune response to immunisations received prior to administration of belimumab.	Exclude patients who have received a live vaccine within 30 days of Day 0.	Do not administer live vaccines concurrently.
Potential psychiatric events – Depression and suicidality	There have been reports of depression and suicidality in patients receiving belimumab. The estimated rates of suicidality for belimumab remain consistent with the rates of the background SLE population. The background rate for completed suicide identified in the literature ranged from 0.02 to 2.18 per 100 PY and varied by study type (clinical trial or observational study) [Li-Yu, 2007; Cervera, 2003; Cervera, 2006; Cervera, 2009]. The background rate for suicidal behavior (completed suicide and attempts) is 0.12 (95% CI 0.05, 0.24)/100 patient years [Karassa, 2003].	Exclude patients who have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months or who in the investigator's judgment, pose a significant suicide risk.	Request that patients report signs and symptoms of psychiatric events including depression and suicidality. Treat appropriately

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 20 subjects will be enrolled to guarantee no less than 12 subjects complete dosing and critical assessments.

4.2. Eligibility Criteria

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

Deviations from inclusion and 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.

4.2.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Subjects who give consent to this study participation and sign informed consent form.
2. Subjects at least 18 years of age inclusive at screening visit.
3. **SLE Classification:** Have a clinical diagnosis of SLE according to the American College of Rheumatology (ACR) classification criteria, with 4 or more of the 11 ACR criteria present, serially or simultaneously during any interval or observation. [Tan, 1982; Hochberg, 1997] (See Appendix 2).
4. **SLE Treatment:** Be on either no SLE medication or a stable SLE treatment regimen of any medication (alone or in combination) for a period of at least 2 months prior to Day 0.
    - Corticosteroids (prednisone or prednisone equivalent, up to 40 mg/day)
    - Immunosuppressive or immunomodulatory agents including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), mizoribine, calcineurin inhibitors (e.g., tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine, or thalidomide.
    - Anti-malarials (e.g., hydroxychloroquine, chloroquine, quinacrine).
    - Non-steroidal anti-inflammatory drugs (NSAIDs)

NOTE:

- For those subjects on alternating day doses of steroids, use the average of 2 daily doses to calculate the average daily steroid dose.

-Low dose prednisone (≤15mg prednisone or equivalent) regular tapering will be acceptable as stable SLE treatment.

5. The subjects with positive test for anti-nuclear antibody (ANA) or anti-dsDNA serum antibody.
6. Males and females. A female subject is eligible to enter the study if at least one of the following conditions apply:

- Not pregnant or nursing;
- 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 tubal ligation); 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 serum pregnancy test at screening, and agree to 1 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 1st dose of IP until study complete; or
    - Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the IP and for 16 weeks after the last dose of IP:
        - Any intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year.
        - Oral contraceptives.
        - 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).
        - Implants of etonogestrel or levonorgestrel;
        - Estrogenic vaginal ring;
        - Injectable progesterone;
        - 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).

7. Based on single or averaged QTc values of triplicate ECGs obtained over a brief recording period:
   - [QTcB or QTcF] <450 msec; or
   - QTcB or QTcF <480 msec in subjects with Bundle Branch Block.

4.2.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. B-cell Therapy: Have received treatment with any B cell targeted therapy (e.g., rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BlyS-receptor fusion protein [BR3], Transmembrane activator and calcium-modulator and cytophilin ligand interactor [TACI] Fc, or belimumab) at any time.
2. The subject has received a biologic investigational or non-investigational agent within 12 months prior to Day 0.
3. Received intravenous immunoglobulin (IVIG), plasmapheresis, hemodialysis, intravenous cyclophosphamide, or high dose prednisone and its equivalents (>60mg/day) within 6 months prior to Day 0.
4. The subject has received a non-biologic investigational agent within 2 months prior to Day 0.
5. The subject is currently participating in another clinical study or post-marketing study in which the subject is or will be exposed to an investigational agent.
6. The subject has severe lupus kidney disease (defined by proteinuria >6g/24h) within 6 months prior to the Screening visit.
7. History of a major organ transplant (eg. heart, lung, renal, liver) or hematopoietic stem cell/marrow transplant.
8. Active CNS lupus [including seizures, psychosis, organic brain syndrome, cerebrovascular accident (CVA), motor neuropathy, vasculitis] requiring medical intervention within 6 months prior to Screening visit.
9. **Infections:** Have required management of acute or chronic infections, as follows:
   - Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
   - Hospitalisation for treatment of infection within 2 months prior to Day 0.

- Use of parenteral (IV or intramuscular [IM]) antibiotics (antibacterials, antivirals, anti-fungals, or anti parasitic agents) within 2 months prior to Day 0.

10. The subject has-IgA deficiency (IgA level <10 mg/Dl).

11. Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.

12. Uncontrolled other diseases: History or clinical evidence of active significant acute or chronic diseases (i.e., cardiovascular, pulmonary, untreated hypertension, anemia, gastrointestinal, hepatic, renal, neurological, cancer, or infectious diseases) which, in the opinion of the investigator, could confound the results of the study or put the subject at undue risk.

13. Have a planned surgical procedure, or a history of any other medical disease, or laboratory abnormalities, or conditions which would make the subject (in the opinion of the Investigator) unsuitable for the study.

14. The subject has an abnormality on 12-lead ECG at screening which is clinically significant in the opinion of the investigator, and which could confound the results of the study. Inclusion may put the subject at undue risk.

15. Have evidence of current drug or alcohol abuse or dependence.

16. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≥2x upper limit of normal (ULN); alkaline phosphatase and bilirubin >1.5xULN (isolated bilirubin >1.5ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

17. Have a historically positive human immunodeficiency virus (HIV) test or test positive at screening for HIV.

18. History of or positive test at screening visit for any of Hepatitis B surface antigen (HbsAg), anti- Hepatitis B core antibody (HbcAb) or anti-hepatitis C virus antibodies (HCVAb). If only anti-HbcAb result is positive, HBV-DNA test will be performed. If hepatitis B virus (HBV)-DNA results in negative, the patient is eligible.

    NOTE: For those subjects included, additional ongoing assessment is required (see Section 6.2.1.1).

19. **Laboratory Abnormalities:** Have a Grade 3 or greater laboratory abnormality based on the protocol toxicity scale [Appendix 3] except for the following that are allowed:

    - Stable Grade 3 prothrombin time (PT) secondary to warfarin treatment.

- Stable Grade 3/4 proteinuria (≤ 6 g/24 hour equivalent by spot urine protein to creatinine ratio allowed).
- Stable Grade 3 hypoalbuminemia due to lupus nephritis, and not related to liver disease or malnutrition.
- Stable Grade 3 neutropenia or stable Grade 3 white blood cell count.

20. Subjects who have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months or who, in the investigator's opinion, pose a significant suicide risk.

21. Received a live vaccine within 30 days of baseline (Day 0).

22. Have a history of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix.

4.2.3. Contraception Requirements

4.2.3.1. Female Subjects

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

Abstinence

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

Contraceptive Methods with a Failure Rate of <1%

- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of etonogestrel or levonorgestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label
- **Documented** male partner sterilization prior to **the female subject's entry** into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's review of the

subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.

- Male condom combined with one of the contraceptive options below:
  - Contraceptive subdermal implant
  - Intrauterine device or intrauterine system
  - Combined estrogen and progestogen oral contraceptive
  - Injectable progestogen
  - Contraceptive vaginal ring Percutaneous contraceptive patches

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

- 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. Withdrawal Criteria and Procedures

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if necessary a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study.

These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the Case Report Form (CRF). If a subject prematurely withdraws from participation in the study for any reason, the investigator/sub-investigator must make every effort to assess the items specified on discontinuation test.

Refer to Section 5.2.1 for Liver Chemistry stopping criteria, Section 5.2.2 for QTc withdrawal and Section 7.2 for Pregnancy.

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). See Section 5.2.1 for details.

4.4. Subject Completion

A subject who participates in all study sessions (including screening, treatment and follow-up) will be considered as having completed the study.

5. STUDY TREATMENT

5.1. Investigational Product and Other Study Treatment

	Study Treatment
Product name:	GSK1550188
Formulation description:	GSK1550188 400 mg per vial plus excipients (citric acid/sodium citrate/sucrose/polysorbate)
Dosage form:	Reconstituted solution
Unit dose strength(s)/Dosage level(s):	400 mg per vial (to contain 80 mg/Ml when reconstituted with 4.8 Ml sterile water for injection [SWFI])
Route/ Administration/ Duration:	Intravenous infusion for over an hour
Physical description:	White uniform lyophilised cake in a 20 Ml vial
Manufacturer/ source of procurement:	Human Genome Sciences, Inc.

5.2. Treatment Assignment

Subjects will be assigned to GSK1550188 10 mg/kg treatment in an open label fashion.

5.2.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Study treatment will be stopped **for a subject** if the following liver chemistry stopping criteria is met:

- ALT ≥3xULN

NOTE: Refer to Appendix 1 for details of the required assessments if a subject meets the above criteria**.**

5.2.2. QTc Withdrawal Criteria

A subject that meets any of the criteria below will be withdrawn from the study. The same QT correction formula (e.g., QT duration corrected for heart rate by Bazett's formula [QTcB], QT duration corrected for heart rate by Fridericia's formula [QTcF]) should be used to determine inclusion and discontinuation for any individual subject throughout the study.

- [QTcB or QTcF] >500 msec,
- [Change from baseline: QTcB or QTcF >60 msec]
- uncorrected QT >600 msec

If a subject has underlying bundle branch block the following withdrawal criteria should be used instead:

Baseline QTc value (with underlying bundle branch block)	QTc withdrawal criteria
<450 msec	>500 msec
450-480 msec	>530 msec

Withdrawal of subjects is to be based on an average corrected QT interval (QTc) value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period of time and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

5.3. Blinding

This will be an open label study.

5.4. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements. Label on each vial and box includes study protocol number, name of investigational drug, serial number, storage condition and study sponsor.

5.5. Preparation/Handling/Storage/Accountability

The 400 mg single use vial of active IP will be reconstituted with 4.8 Ml SWFI, to yield a final concentration of 80 mg/Ml of GSK1550188. After reconstitution the material is stable for up to 8 hours at 2-8°C, or at room temperature.

All IPs must be stored in a secure area with access limited to the investigator and authorized site staff and under physical conditions that are consistent with IP-specific requirements. All treatment packs will be stored refrigerated at 2-8ºC. Maintenance of a temperature log (manual or automated) is required. Only authorized site staff may supply or administer IP. IP must be dispensed or administered according to procedures described

herein. Only subjects enrolled in the study may receive IP, in accordance with all applicable regulatory requirements.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance. The investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain study treatment accountability records throughout the course of the study. The responsible person(s) will document the amount of study treatment received from and returned to GSK and the amount supplied and/or administered to and/or returned by subjects. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused study treatment are listed in the study procedures manual (SPM).

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 infusion. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgement. 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 the infusion.

For subjects who have previously received IVIG or subjects with a history of allergies (allergic responses to food, drugs, insects, or a history of urticaria), diphenhydramine (12.5 to 50 mg based on clinical judgment) or equivalent and paracetamol (acetaminophen), should be administered prophylactically, prior to dosing. Antihistamine H2-receptor antagonists (e.g., ranitidine) are also permitted. Sites are encouraged to follow their standard practices to manage any untoward infusion reactions noted during the infusion period.

5.5.1. Occupational Safety

Under normal conditions of handling and administration, the IP is not expected to pose significant safety risks to site staff.

Adequate precautions must be taken to avoid direct eye or skin contact and to avoid the generation of aerosols or mists. The monitor must be notified of any unintentional occupational exposure.

The Procedures for Handling Ips describing the occupational hazards and recommended handling precautions will be provided to site staff.

5.6. Assessment of Compliance

When the individual dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When subjects are dosed at the study site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

5.7. Concomitant Medications and Non-Drug Therapies

5.7.1. Permitted Medications

Use of the medications may be continued if they have been used before the screening visit. Their dosage and administration, however, should be unchanged during the screening period.

Once the subject is enrolled and receives belimumab on Day 0, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically required. For subjects with a history of allergies, allergic responses to food, drugs or insects, or a history of urticaria, antihistamine and acetaminophen may be administered prophylactically.

All prescription and over-the-counter medications (including herbal medicines) that have been taken within 60 days prior to the first infusion of study treatment and all concomitant medications taken during the study will be recorded in the CRF.

5.7.2. Prohibited Medications and Non-Drug Therapies

The following medications and therapies are prohibited:

From 12 months prior to Day 0:

- Biologic investigational and non-investigational agent

From 6 months prior to Day 0:

- Hemodialysis
- Intravenous cyclophosphamide (Cytoxan)
- High-dose prednisone (>60 mg/day)
- IVIG
- Plasmapheresis

From 2 months prior to Day 0:

- Non-biologic investigational agent.
- Corticosteroids (prednisone or prednisone equivalent, >40 mg/day)
- Parenteral antibiotics

From 30 days prior to Day 0

- Live vaccine

During the study period:

- 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- tumour necrosis factor (TNF) or anti-interleukin-6 (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.
- Live vaccine.

6. STUDY ASSESSMENTS AND PROCEDURES

A schedule of study assessments and tests is shown in Table 2. The details of study assessments are shown in "Study Procedures Manual" that sponsor prepared separately.

The time assessment window of the each PK blood sample collection is shown in Table 3. The end time of the infusion will be designated Time 0, and subsequent PK sampling and safety assessments will be performed relative to this time. It is essential that the exact time of blood sampling, however, should still be accurately recorded. The safety assessments are recommended to be conducted close to PK sample collection; however, when several procedures are scheduled at the same nominal time point, PK blood sampling should be given priority.

Table 2 Time and Events Table

Visit	1	2						3	4	5	6	7	8	9	10	
Day	Screening Day -30 to -1	Day 0						Day 1	Day 7	Day 14	Day 21	Day 28	Day 42	Day 56	Day 84	Discontinuation[11]
		Pre	0	5m	1h	6h	24h									
Informed consent[1]	X															
Medical History	X	X														
Demography	X															
Inclusion/Exclusion criteria	X	X[2]														
Complete physical examination, including Height	X															
Body weight		X														
Vital signs[3]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory test[4]	X	X[4]					X			X		X		X	X	X
Spot urine (protein to creatinine ratio)	X															
Urine drug/alcohol screen	X															
HIV, Hepatitis B, C[5]	X															
Pregnancy test (women)[6]	X	X[4]										X			X	X
Chest X ray	X															
12 lead ECG	X	X[4]					X								X	X
Biological Markers[7]	X[8]	X								X		X	X	X	X	
Blood PK sampling		X		X	X	X	X	X	X	X	X	X	X	X	X	

Visit	1	2						3	4	5	6	7	8	9	10	
Day	Screening Day -30 to -1	Day 0						Day 1	Day 7	Day 14	Day 21	Day 28	Day 42	Day 56	Day 84	Discontinuation[11]
		Pre	0	5m	1h	6h	24h									
AE/SAE Review[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Admission to Unit		X[10]														
Dosing			X													
Discharge							X[10]									
Outpatient Visit	X							X	X	X	X	X	X	X	X	X

1. Each subject must sign an informed consent form prior to undergoing any Screening assessments.
2. Clinical laboratory test at screening visit will be used for inclusion/exclusion criteria check.
3. Vital signs include temperature, sitting blood pressure and heart rate. Pulse rate could be used to replace heart rate monitoring if subject has regular sinus rhythm.
4. Clinical Laboratory test include hematology, chemistry and urinalysis (including C-reactive protein [CRP] and Erythrocyte Sedimentation Rate on screening). ALT and/or AST elevations of greater than 2.5 x ULN will require additional Hepatitis B assessment, see Section 6.2.1.1. For pre-dose safety lab monitoring including urine pregnancy test and 12 lead ECG, it's recommended to be done on day 0 or within 48 hours prior to day 0 if site logistic management are limited on day 0 for drug dosing and intensive PK sample collection.
5. HIV antibody, Hepatitis B surface antigen, anti-HBc and Hepatitis C antibody.
6. Pregnancy should be assessed with a blood test at Screening and with a urine test during the treatment period. Pregnancy beyond Day 84 and within 16 weeks after last dose of IP will be assessed with a homekit and subjects can report the results via phone to site.
7. Biomarkers include immunoglobulins, 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).
8. Only immunoglobulins (IgG, IgM and IgA) and auto antibodies (anti-dsDNA, ANA).
9. Includes subject history to be reported on CRF regarding any general signs or symptoms of infection.
10. The recommended date of "Admission to the Unit" and "Discharge" is only a suggestion. The subject can be admitted to unit from Day -2 to Day 0 and/or discharged on Day 1 based on site flexibility and resource allocation.
11. If a subject prematurely withdraws for any reason, the investigator must make every effort to assess the items specified on discontinuation test.

Table 3 Time assessment window of the each PK sample collection

Study Day	Hrs relative to dose	Blood sampling for PK
Day 0: pre-dose	Day 0 pre-dose	-60 minutes
Day 0: 5min	5min after dose completion	± 1 minutes
Day 0: 1hour	1 hour after dose completion	± 10 minutes
Day 0: 6 hour	6 hour after dose completion	± 15 minutes
Day 0: 24 hour	24 hour after dose completion	± 1 Hrs
Day 1	48 hour after dose completion	± 2 Hrs
Day 7	192 hour after dose completion	-48Hrs to +2 Hrs
Day 14	360 Hrs after dose completion	-48Hrs to +2 Hrs
Day 21	528 Hrs after dose completion	-48Hrs to +2 Hrs
Day 28	696 Hrs after dose completion	-48Hrs to +2 Hrs
Day 42	1032 Hrs after dose completion	-48Hrs to +2 Hrs
Day 56	1368 Hrs after dose completion	-48Hrs to +2 Hrs
Day 84	2040 Hrs after dose completion	-48Hrs to +2 Hrs

6.1. Critical Baseline Assessments

A signed written informed consent form must be obtained prior to Screening assessments, and before any study-specific assessments for Baseline assessments are initiated.

Baseline level is the basal value required for comparing examination/observation data after the infusion of investigational drug. Therefore, the examination at pre-dose is normally performed. If the data are not examined at Day 0, values at screening will be used as baseline levels.

6.1.1. Screening Test

During the screening visit, each subject will have the following evaluations to determine eligibility for enrollment:

- Demographic information including gender, ethnic origin, race, date of birth.
- Medical history, including cardiovascular history and risk factors.
- Complete physical examination, including height.
- Vital signs including temperature, sitting blood pressure, and heart rate.
- Confirm classification of SLE disease (based on ACR criteria) by reviewing previously documented clinical records.
- Clinical laboratory tests:
    - Hematology: White blood cells (WBC), Red blood cells (RBC), Hemoglobin (Hb), Hematocrit (Ht), platelet count and WBC-differential

- Chemistry: AST, ALT, Alkaline phosphatase (ALP), Gamma glutamyltransferase (GGT), Lactate dehydrogenase (LDH), creatinine, Blood urea nitrogen (BUN), total bilirubin, total protein, albumin, uric acid, Prothrombin time (PT), Partial Thromboplastin Time (PTT), Erythrocyte Sedimentation Rate (ESR), CRP, glucose, sodium, potassium, magnesium, chloride, carbon dioxide (CO2), calcium, phosphate
- Urinalysis: protein, glucose, ketones, occult blood, microscopic examination
- Spot urine for proteinuria assessment

- Urine drug/alcohol screen.
- HIV antibody, Hepatitis B surface antigen, anti-HBc, HBV DNA and Hepatitis C antibody.(NOTE: if anti-HBc result is reactive, the sample drawn for HBV DNA will be tested for viral DNA; otherwise, the sample will be destroyed).
- Serum Pregnancy test.
- Chest X ray.
- 12-lead ECG.
- Immunoglobulins (IgG, IgM and IgA) and auto antibodies (anti-dsDNA, ANA).
- Adverse events.

6.1.2. Pre-dose Examination

Pre-dose examination will be conducted before the dose:

- Adverse events.
- Body weight.
- Vital signs including temperature, sitting blood pressure, and heart rate.
- Current medical history.
- Clinical laboratory tests: hematology, chemistry and urinalysis.
- Urinary pregnancy test (for female only).
- 12-lead ECG.
- Inclusion/exclusion criteria check
- PK blood sampling.

- 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)

6.2. Safety

The following will be made as the safety assessments.

- Adverse events.
- Clinical laboratory tests: hematology, chemistry and urinalysis.
- Vital signs (blood pressure, heart rate and body temperature).
- 12-lead ECG.

6.2.1. Liver Chemistry Follow-up Procedures

Liver chemistry withdrawal criteria have been designed to assure subject safety and evaluate liver event etiology.

Liver chemistry stopping criteria 1-3 are defined below:

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

NOTE: if serum bilirubin fractionation is not immediately available, study drug 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 ≥5xULN.

3 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.

When any of the liver chemistry withdrawal criteria is met, do the following:

- 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 bilirubin) (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, study drug 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.

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 and 3:

- 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 ≥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.
- 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 1-3, 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 ribonucleic acid (RNA);
    - Cytomegalovirus IgM antibody;
    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
    - Hepatitis E IgM antibody
- Blood sample for pharmacokinetic (PK) analysis, obtained within 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 IP prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of 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, total IgG.

- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

6.2.1.1. Additional Hepatitis B Monitoring

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

- ALT and/or AST elevations of greater than 2.5 x ULN will require:
  - Sites to review screening laboratory results for anti-HBc:
    - If screening anti-HBc result was reactive, then obtain HBV DNA.
      - If HBV DNA returns reactive, investigator will determine the extent of required attention for proper follow up of potential hepatitis B re-activation.
    - If screening anti-HBc result was negative, then repeating hepatitis B testing is optional per investigator upon investigating for other causes.

  Refer to the SPM for guidance on documenting the suspected reason for ALT and/or AST elevations of greater than 2.5 x ULN.

6.2.2. Clinical Laboratory

Blood and urine will be taken for clinical laboratory test at screening and at pre-dose, and Days 0, 1, 14, 28, 56 and 84 post-dose.

- Hematology: WBC, RBC, Hb, Ht, PT, PTT, platelet count and WBC-differential (including ESR on screening)
- Chemistry: AST, ALT, ALP, GGT, LDH, creatinine, BUN, total bilirubin, total protein, albumin, uric acid, glucose, sodium, potassium, magnesium, chloride, carbon dioxide, calcium, phosphate (including CRP on screening)
- Urinalysis: protein, glucose, ketones, occult blood, microscopic examination
- Spot urine for proteinuria assessment

Note: ALT and/or AST elevations of greater than 2.5 x ULN will require Hepatitis B assessment, see Section 6.2.1.1

All clinical laboratory blood samples will be sent to a central laboratory for analysis (details provided in the SPM). The central laboratory will fax laboratory results to the Investigator and will transmit the results electronically to GlaxoSmithKline.

6.2.3. Vital Signs

Systolic and diastolic blood pressure (sitting), heart rate, and body temperature will be measured. Measurements of vital signs will be taken at screening and at pre-dose, and at 5 minutes, 1, 6 and 24 hours, and Days 1, 7, 14, 21, 28, 42, 56 and 84 post-dose.

At the discretion of the Investigator, vital signs may be assessed at unscheduled visits.

6.2.4. 12-Lead ECG

Measurements of 12-Lead ECG will be taken at screening and at pre-dose, and 24 hours and Day 84 post-dose. The ECG parameters are HR, PR, QRS, QT and QTc.

6.3. Pharmacokinetics

Blood samples will be collected for PK at pre-dose, and at 5 minutes, 1, 6 and 24 hours, and Days 1, 7, 14, 21, 28, 42, 56 and 84 post-dose. The actual date and time of sampling will be recorded in the CRF. Serum will be harvested within one hour of blood sample collection. PK samples will be sent to a local bioanalytical laboratory and analyzed using a validated method (details provided in the SPM).

6.4. Pharmacodynamic/Biomarkers

Blood samples will be collected at screening and at pre-dose, Days 14, 28, 42, 56 and 84 post-dose. The actual date and time of sampling will be recorded in the CRF. All blood samples will be sent to a central laboratory for analysis (details provided in the SPM). The central laboratory will fax the results to the Investigator and will transmit the results electronically to GlaxoSmithKline.

- 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).

7. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, PREGNANCY AND MEDICAL DEVICE INCIDENTS

7.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

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

7.1.1. Time period for collecting AEs and SAE information

AEs will be collected from the start of Study Treatment and until the Day 84 or study discontinuation. Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions CRF.

Serious AEs will be recorded from the time the consent form is signed until the follow-up contact. All SAEs will be recorded and reported to GSK within 24 hours.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator would promptly notify GSK.

7.1.2. Definition of Adverse Events

An AE is 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.

Events meeting the definition of an AE **include**:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.).

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

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- 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.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure are 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.

7.1.3. Definition of Serious Adverse Events

If an event is not an AE per Section 7.1.2, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

An SAE is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in disability/incapacity, or

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

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Is associated with liver injury **and** impaired liver function defined as:

- ALT ≥3xULN and total bilirubin* ≥2xULN (>35% direct), **or**
- ALT ≥3xULN and INR** >1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥3xULN and total bilirubin ≥2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

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

Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as Aes or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as Aes or SAEs.

7.1.5. Method of Detecting AEs and SAEs

The investigator (or sub-investigators) will do the medical examination following the schedule with nondirective interview such as the following sentences.

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.1.6. Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the CRF. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the appropriate AE/SAE CRF pages. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

7.1.7. Evaluating AEs and SAEs

The definition of an AE and a SAE is provided in Section 7.1.2 and Section 7.1.3.

7.1.8. Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on Division of Microbiology and Infectious Diseases (DMID) Adverse Event Severity Grade Tables (see Appendix 3), 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 is 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.

7.1.9. Assessment of Causality

The investigator (or sub-investigator) is obligated to assess the relationship between IP and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator (or sub-investigator) will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the IP will be considered and investigated. The investigator (or sub-investigator) will also consult the IB and/or Product Information, in the determination of his/her assessment. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator (or sub-investigator) has minimal information to include in the initial report to GSK. However, it **is very important that the investigator (or sub-investigator) always make an assessment of causality for every event prior to the initial transmission of the SAE**

data to GSK. The investigator (or sub-investigator) may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator (or sub-investigator) will provide the assessment of causality as per the instructions for completion of the AE/SAE data collection tool.

7.1.10. Completion and Transmission of SAEs Report

Once an investigator (or sub-investigator) becomes aware that an SAE has occurred in a study subject, she/he will report the information to GSK within 24 hours or as outlined in the protocol in the section titled, "Prompt Reporting of Serious Adverse Events and Other Events to GSK". The SAE data collection tool will always be completed as thoroughly as possible with all available details of the event, and submitted to GSK within the designated time frames. If the investigator (or sub-investigator) does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the appropriate data collection tool. The appropriate data collection tool will be updated when additional information is received.

The investigator (or sub-investigator) will always provide an assessment of causality at the time of the initial report as described in the section of this document titled, "Assessment of Causality".

The primary mechanism for reporting SAEs to GSK will be the electronic data collection (EDC) tool (e.g., InForm system). If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to GSK. The site will then enter the serious adverse event data into the electronic system as soon as it becomes available.

GSK will provide a separate list of contact details for reporting SAEs, including fax numbers and telephone numbers.

7.1.11. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator (or sub-investigator) is required to proactively follow each subject and provide further information to GSK on the subject's condition. All Aes and SAEs documented at a previous visit/contact and that are designated as ongoing, will be reviewed at subsequent visits/contacts.

All Aes and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. This applies to all subjects, including those withdrawn prematurely. The investigator (or sub-investigator) will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

GSK may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator (or sub-investigator) is obligated to assist. If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology (may not be required for studies where death is an endpoint).

New or updated information will be recorded in the originally completed SAE data collection tool. The investigator (or sub-investigator) will submit the updated SAE data to GSK within the designated reporting time frames.

7.1.12. Post-study AEs and SAEs

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE detection period as defined in the protocol.

Investigators (or sub-investigator) are not obligated to actively seek AEs or SAEs in former subjects. However, if the investigator (or sub-investigator) learns of any SAE, including a death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the IP or study participation, the investigator (or sub-investigator) will promptly notify GSK.

After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data. If the site is notified of a new SAE from a subject or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, the site can report this information on the paper SAE data collection tool or to their GSK protocol contact by telephone.

7.1.13. Prompt Reporting of SAEs to GSK

SAEs, pregnancies, medical device incidents, 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.

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE contactor.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the ‘reviewed’ box at the bottom of the eCRF page within 72 hours of submission of the SAE.

- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to SAE contactor by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

Table 4 Reporting of SAE and Other Events to GSK

	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≥3xULN 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

	Initial Reports		Follow-up Information on a Previous Report	
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.
The method of 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.

7.1.14. 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 regulatory authorities, IRBs/IECs 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 an 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 Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), if appropriate according to local requirements.

7.2. Pregnancy

Any pregnancy that occurs during study participation and for 16 weeks following last dose must be reported using a clinical trial pregnancy form. For pregnancy occurring after the last visit but within 16 weeks after last dose, it can be reported by subjects using a phone call. 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 (or sub-investigator's) attention after the subject has completed the study and considered by the investigator (or sub-investigator) as possibly related to the IP, must be promptly reported to GSK.

If a subject has a positive pregnancy test during study participation, complete a Pregnancy Notification Form and fax it to GSK. Follow the subject to determine the outcome of the pregnancy and forward the outcome information using a Pregnancy Follow-up Form to GSK no later than 6 to 8 weeks following the estimated delivery date.

7.3. PML

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, consideration should be given to stopping immunosuppressant therapy. **If PML is suspected, this should be immediately reported to the Medical Monitor.**

8. DATA MANAGEMENT

For this study subject data will be collected using GSK defined case report forms 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 (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSK Drug. Original CRFs will be retained by GSK, while the investigator will retain a copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Full details of tabulation/analyses will be described in the "Reporting Analysis Plan" (RAP).

Any changes form analyses described within this protocol will be stated in "RAP" and "Final Clinical Study Report"

If the study is prematurely discontinued, all available data will be listed and a review will be carried out to assess which statistical analyses are still considered appropriate.

Data obtained for this study and used for statistical analysis will be examined for outliers, and their accuracy will be verified or queried. Values verified as accurate will be included in the analysis.

All categorical data will be summarized by reporting the frequency and percentage of subjects in each cohort.

All continuous data will be summarized using mean, standard deviation, median, ranges, and 95% confidence interval (CI) where applicable.

9.1. Hypotheses and Treatment Comparisons

The primary objective of this study is to evaluate the pharmacokinetics of single dose GSK1550188 in Chinese subjects with SLE. No formal statistical hypothesis testing will be conducted; however, summaries of safety parameters, PK, and PD will be provided.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

There are no formal calculations of power or sample size for this study. The sample size of 20 to obtain 12 evaluable subjects has been chosen based on feasibility, as well as to meet requirement of China FDA, 2005 (CFDA Guidance).

With 12 evaluable subjects in this study, assuming that the CV% of Cmax and AUC(0-inf) is 20.0% and 32.1% respectively (from study C1105), it is estimated that the lower and upper bounds of the 95% confidence interval would lie within 13.4% of the point estimate for Cmax and 22.0% of the point estimate for AUC(0-inf). This is narrower than the Japan study BEL114243, in which the 95% confidence interval lied within 15.0% of the point estimate for Cmax and 33.7% of the point estimate for AUC (0-inf).

9.2.2. Sample Size Sensitivity

No sample size sensitivity analysis will be performed.

9.2.3. Sample Size Re-estimation

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

9.3.1. Analysis Population

All subjects who receive the study medication will be included in the safety population.

All subjects who receive the study medication and for whom a pharmacokinetic sample is obtained will be included in the pharmacokinetic concentration population.

All subjects who receive a dose of GSK1550188 and for whom pharmacokinetic parameters can be calculated will be included in the pharmacokinetic parameter population.

All subjects who receive the study medication and for whom pharmacodynamic data is available will be included in the pharmacodynamic population.

If any subject is excluded from analyses, the details and reason will be described in the final study report.

9.3.2. Analysis Data Set

All available data will be included in the data sets.

9.3.3. Interim Analysis

No formal interim analysis is planned.

9.3.4. Final Analyses

9.3.4.1. Safety Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. Summaries of safety data (adverse events and the results of examinations) will include adverse events, serious adverse events, vital signs, ECG and laboratory parameters.

9.3.4.1.1. Extent of Exposure

The date and time of study drug administration will be listed.

9.3.4.1.2. Adverse Events

Adverse events will be coded using (MedDRA) and summarized by System Organ Classes (SOCs) and Preferred Term. A summary of the number and percentage of subjects with Aes occurring on or after the treatment start date will be displayed.

9.3.4.1.3. Clinical Laboratory Evaluations

For clinical laboratory data, summary statistics will be provided for each laboratory parameter and listings showing time courses will be prepared. Change from baseline data will also be summarized.

Data exceeding the reference values will be listed.

9.3.4.1.4. Vital Signs

For systolic and diastolic blood pressure and heart rate, summary statistics will be provided and listings showing time courses will be prepared. Change from baseline data will also be summarized.

9.3.4.1.5. 12-Lead ECG

All 12-lead ECG data will be listed and summarised in the same manner as described above for blood pressure and heart rate. The ECG parameters, HR, PR, QRS, QT and QTc, will be presented in the summary table.

9.3.4.2. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modeling & Simulation department within GlaxoSmithKline.

9.3.4.2.1. Serum Concentrations

Serum concentrations of GSK1550188 at each assessment point will be listed to prepare figures showing individual concentration-time profiles on both linear and semi-log scales. In addition, the mean and median serum concentrations at each assessment point will be calculated from concentration data of individual subjects to prepare figures showing mean and median serum concentration-time profiles on both linear and semi-log scales.

9.3.4.2.2. Pharmacokinetic Parameters

Serum concentration-time data for GSK1550188 will be analyzed by non-compartmental methods using WinNonlin 5.2 or above. Calculations will be based on the actual dose and sampling dates and times recorded during the study. From the concentration-time data for GSK1550188, the following pharmacokinetic parameters will be determined: maximum concentration (Cmax), area under the plasma concentration-time curve [AUC(0-t) and AUC(0-∞)], and apparent terminal phase half-life (t1/2), terminal phase elimination rate (λz), systemic clearance (CL), and volume of distribution (Vz). Summary statistics for the above parameters will be calculated.

For each of the derived serum GSK1550188 pharmacokinetic parameters, the following summary statistics will be calculated: median, minimum, maximum, arithmetic mean, standard deviation, coefficient of variation, geometric mean, 95% confidence interval for the geometric mean and standard deviation of logarithmically transformed data.

9.3.4.3. Pharmacodynamic/Biomarker Analyses

Estimates of percent change from baseline for B cell subsets will be performed in the PD population. Full details of analyses of PD will be outlined in the "RAP". The data of the PD population will be summarised. All derived parameters will be listed and summarized.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

The study will also be conducted in accordance with International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent (and any amendments) to be obtained for each subject before participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

Written informed consent must be obtained from each subject prior to participation in the study.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including 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 also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify 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

10.4. Quality Assurance

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

10.5. Study and Site Closure

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK procedures.

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites. If GSK determines such action is needed, GSK will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action. When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform investigators or the head of the medical institution (where applicable) and the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The

investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or GSK standards/procedures; otherwise, the retention period will default to 25 years.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator leaves the site.

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

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

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

The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

11. REFERENCES

Boers A, Li Q, Wong M, Miller M, Littlejohn G. Differences in SLE disease activity between patients of Caucasian and South-East Asian/Chinese background in an Australian hospital. *APLAR Journal of Rheumatology.* 2006;9:43-48.

Brocard A, Barbarot S, Milpied B, Stalder JF. Thalidomide in the treatment of chronic discoid lupus erythematosus. *Ann Dermatol Venereol.* 2005;132(11 Pt 1):853-6.

Carter RH. A role for BlyS in tissue inflammation?. *Arthritis Rheum.* 2003;48(4):882-5.

Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine 2003;82(5):299-308.

Cervera R, Khamashta MA, Hughes GRV. The Euro-lupus project: epidemiology of systemic lupus erythematosus in Europe. Lupus 2009;18:869-74.

Cervera R. Systemic lupus erythematosus in Europe at the change of the millennium: Lessons from the "Euro-Lupus Project". Autoimmun Rev 2006;5:180-6.

Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. *Arthritis Rheum.* 2007;56:2092-4.

Chatham WW, Kimberly RP. Treatment of lupus with corticosteroids. *Lupus.* 2001;10(3):140-7.

Cheema DS, Roschke V, Hilbert DM, Stohl W. Elevated serum B-lymphocyte stimulator levels in patients with systemic immune-based rheumatic diseases. *Arthritis Rheum.* 2001;44(6):1313-9.

China FDA, 2005, Technical guidance for clinical pharmacokinetics study of chemical drugs

Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Tables, May 2001. http://www.niaid.nih.gov/dmid/clinresearch/DMIDadulttox.doc

Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, P *et al*. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med.* 2005;353(21):2219-28.

GlaxoSmithKline Document Numbers 2011N128591_01, Belimumab Investigator's Brochure , 20-JUN-2013,version 11

Govoni M, Castellino G, Bosi S, Napoli N, Trotta F. Incidence and prevalence of systemic lupus erythematosus in a district of North Italy. *Lupus.* 2006;15:110-13.

Gross J, Dillon S, Mudri S, Johnston J, Littau A, Roque R, *et al*, TACI-Ig neutralizes molecules critical for B cell development and autoimmune disease. Impaired B-cell maturation in mice lacking BlyS. *Immunity.* 2001;15(2):289-302.

Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1997;40(9):1725.

Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido ER, Danieli, MG, *et al*. Early Response to Immunosuppressive therapy predicts good renal outcome in lupus nephritis. *Arthritis Rheum*. 2004;50(12):3934-40.

Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido ER, Danieli, MG, *et al*. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum.* 2002;46(8):2121-31.

Illei GG, Austin HA, Crane M, Collins L, Gourley MF, Yarboro CH, *et al*. Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. *Ann Intern Med.* 2001;135(4):248-57.

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

Khare SD, Sarosi I, Xia XZ, McCabe S, Miner K, Solovyev I, *et al*. Severe B-cell hyperplasia and autoimmune disease in TALL-1 transgenic mice. *Proc Natl Acad Sci USA.* 1999;97:3370-5.

Liossis SN, Kovac B, Dennis G, Kammer GM, Tsokos GC. B cells from patients with systemic lupus erythematosus display abnormal antigen receptor-mediated early signal transduction events. *J Clin Invest.* 1996;98(11):2549-57.

Lipsky PE. Systemic lupus erythematosus: an autoimmune disease of B cell hyperactivity. *Nature Immunology.* 2001;2(9):764-6.

Li-Yu J, Navarra SV. A survey of psychosocial attributes of Filipino patients with systemic lupus erythematosus. APLAR Journal of Rheumatology 2007;10:107-111.

Lopez P, Mozo L, Gutierrez C, Suarez A. Epidemiology of systemic lupus erythematosus in a northern Spanish population: gender and age influence on immunological features. *Lupus.* 2003;12:860-65.

Mackay F, Woodcock SA, Lawton P, Ambrose C, Baetscher M, Schneider P, et al,. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. *J Exp Med.* 1999;190:1697-10.

Mok CC, Lau CS. Lupus in Hong Kong Chinese. *Lupus.* 2003;12:717-22.

Moore PA, Belvedere O, Orr A, Pieri K, Lafleur DW, Feng P, *et al*. BlyS: member of the tumor necrosis family and B lymphocyte stimulator. *Science.* 1999;285(5425):260-3.

Naleway AL, Davis ME, Greenlee RT, Wilson DA, McCarty DJ. Epidemiology of systemic lupus erythematosus in rural Wisconsin. *Lupus.* 2005;14:862-66.

National Women's Health Information Center (NWHIC), 2003; US Department of Health and Human Services. Available on-line at www.hhs.gov

Nightingale AL, Farmer RDT, de Vries CS. Systemic lupus erythematosus prevalence in the U.K.: methodological issues when using the General Practice Research Database to estimate frequency of chronic relapsing-remitting disease. *Pharmacoepidemiology and Drug Safety.* 2006;16:144-51.

Office of Minority Health Resource Center (OMHRC), HHS 2001. Available on-line at http://www.omhrc.gov.

Petri M. Systemic lupus erythematosus: clinical aspects. In: Koopman W, editor. *Arthritis and Allied Conditions: A Textbook of Rheumatology. 14th ed.* Philadelphia, PA:Lippincott Williams and Wilkins, 2001:1455-79.

Pisetsky DS. Systemic lupus erythematosus: epidemiology, pathology, and pathogenesis. In: Arthritis Foundation, editor. *Primer on the Rheumatic Diseases.* Atlanta:Arthritis Foundation, 2001:17:329-35.

Reveille JD. The treatment of systemic lupus erythematosus. In: Koopman W, editor. *Arthritis and Allied Conditions: Textbook of Rheumatology. 14th ed.* Philadelphia, PA:Lippincott Williams and Wilkins, 2001:1533-45.

Ruiz-Irastorza G, Khamashta M, Castellino G, Hughes GR. Systemic lupus erythematosus. *Lancet.* 2001;357(9261):1027-32.

Tan EM, Cohen AS, Fries JF, Masi AT, Mcshane DJ, Rothfield NF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982;25(11):1271-7.

Wallace DJ. Management of lupus erythematosus: recent insights. *Current Opinions in Rheumetology.* 2002;14:212-9.

Xiang Y-J, Dai S-M. Prevalence of rheumatic diseases and disability in China. *Rheumatology International.* 2009;29:481-90.

Zhang J, Roschke V, Baker KP, Wang Z, Alarcón GS, Fessler BJ, et al. Cutting edge: A role for B lymphocyte stimulator in systemic lupus erythematosus. *J Immunol.* 2001;166:6-10.

12. APPENDICES

12.1. Appendix 1: Liver Safety Process

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 5.2.1:

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to confirm the subject's study treatment cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 7.1.3), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up withdraw the subject from the study unless further safety follow up is required
- Do not restart study treatment
- Refer to the Flow chart for a visual presentation of the procedures listed below.

Safety Follow-Up Procedures for subjects with ALT ≥3xULN:

- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for subjects with ALT ≥3xULN and total bilirubin ≥2xULN (>35% direct bilirubin); or ALT ≥3xULN and INR[1] >1.5

- This event is considered an SAE (see Section 7.1.3). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

In addition, for all subjects with ALT ≥3xULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody.

[1] INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants.

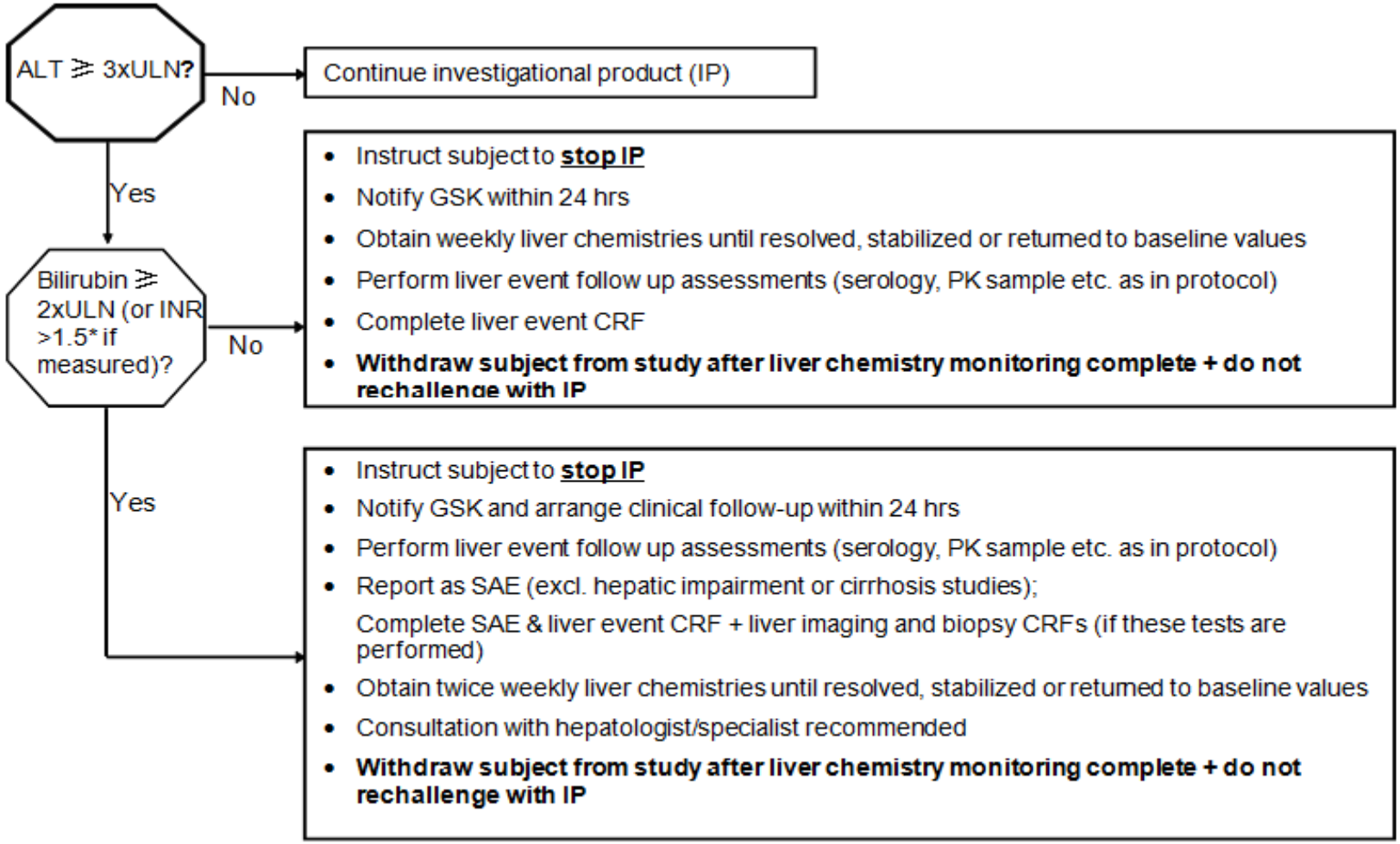
- Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
- Hepatitis C RNA.
- Cytomegalovirus IgM antibody.
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
- Hepatitis E IgM antibody.

- Blood sample for pharmacokinetic (PK) analysis, obtained as per the Time and Events Table (Table 2) of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, **do not obtain a PK sample**. Instructions for sample handling and shipping are included in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the AE CRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.
- Record alcohol use on the Liver Events CRF.

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, total IgG.
- Serum acetaminophen adduct high-performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week).
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

Refer to the diagram below for a visual presentation of the procedures listed above.



*INR threshold does not apply to subjects receiving anticoagulants.

12.2. Appendix 2: American College of Rheumatology (ACR) Criteria for SLE

The ACR Criteria for the Classification of Systemic Lupus Erythematosus* [Tan, 1982; Hochberg, 1997]

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

Criterion	Definition
	positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization (TPI) or fluorescent treponemal antibody (FTA) absorption test.
11. Antinuclear antibody (ANA)	Abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome.

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

References

Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1997;40(9):1725.

Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982;25(11):1271-7.

12.3. Appendix 3: 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

12.3 Appendix 3: 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

12.3 Appendix 3: 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 (non fasting & 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

12.3 Appendix 3: 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

12.3 Appendix 3: 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

12.3 Appendix 3: Adverse Event and Laboratory Value Severity Grade Tables (continued)

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
RESPIRATORY	MILD	MODERATE	SEVERE	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; Forced expiratory volume in 1 second (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 oxygen (O2) therapy

12.3 Appendix 3: Adverse Event and Laboratory Value Severity Grade Tables (continued)

URINALYSIS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proteinuria				
Dipstick Protein	1 +	2-3 +	4 +	Nephrotic syndrome
Spot Urine: Protein:Creatinine Ratio mg/mg	0.2-1.0	>1.0-2.0	>2.0-3.5	>3.5
24 Hour Urine: Protein	200 mg – 1g loss/day	>1-2 g loss/day	>2-3.5 g loss/day	Nephrotic syndrome OR >3.5 g loss/day
Hematuria	Microscopic only >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

12.3 Appendix 3: 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

12.3 Appendix 3: 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 i.e., 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, (i.e., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment mod de-sensation, (i.e., 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 (i.e., upper and lower extremities)	Sensory loss involves limbs and trunk

(concluded)

Modified from DMID Adult Toxicity Tables, 2001

References

Eibl MM, Rosen FS. Intravenous gamma globulin and plasmapheresis. In: Frank MM, editor. *Samter's Immunologic Diseases (5th ed.)*. Boston:Little, Brown, 1995:1529-36.

Goldfarb NS, Avery RK, Goormastic M, Mehta AC, Schilz R, Smedira N, Pien L, Haug MT, Gordon SM, Hague LK, Dresing JM, Evans-Walker T, Maurer JR. Hypogammaglobulinemia in lung transplant recipients. *Transplantation.* 2001;71(2):242-6.

Yamini MH, Avery RK, Mawhorter SD, Young JB, Ratliff NB, Hobbs RE, McCarthy PM, Smedira NG, Goormastic M, Pelegrin D, Starling RC. Hypogammaglobulinemia following cardiac transplantation: a link between rejection and infection. *J Heart Lung Transplant.* 2001;20(4):425-30.

12.4. Appendix 4: Protocol Changes

Protocol amendment 01 applies to all sites.

Section	Previous Text	Revised Text	Rationale
Sponsor/medical monitor Information Page		Deletion of PPD from medial monitor contact information.	Change of Medical Monitor contact information
Section 3.4 Benefit-Risk Assessment	**Table 1-Column "Strategy-monitoring " for infection** Monitor patients for signs and symptoms of infection, monitor laboratory values, request that patients report signs of infection. Treat infections immediately and appropriately. If patient becomes hepatitis B core antibody positive and/or develop an ALT and/or AST >2.0 x ULN, obtain quantitative hepatitis B virus DNA. If the quantitative hepatitis B virus DNA result shows detectable viral loads, then the subject must be treated immediately and appropriately.	Monitor patients for signs and symptoms of infection, monitor laboratory values, request that patients report signs of infection. Treat infections immediately and appropriately. If patient becomes hepatitis B core antibody positive and/or develop an ALT and/or **AST >~~2.0~~ 2.5 x ULN,** obtain quantitative hepatitis B virus DNA. If the quantitative hepatitis B virus DNA result shows detectable viral loads, then the subject must be treated immediately and appropriately.	To keep consistency among Table 1 and Section 6.2.1.1

Section	Previous Text	Revised Text	Rationale
Section 4.2.1 Inclusion Criteria	**4. SLE treatment:** **NOTE:** -For those subjects on alternating day doses of steroids, use the average of 2 daily doses to calculate the average daily steroid dose.	**Add:** **NOTE:** -For those subjects on alternating day doses of steroids, use the average of 2 daily doses to calculate the average daily steroid dose. **-Low dose prednisone (≤15mg prednisone or equivalent)) regular tapering will be accepted as stable SLE treatment.**	Clarify the regular tapering of low dose prednisone is acceptable for enrolment.
Section 4.2.2 Exclusion Criteria	7. History of renal transplant.	7. History of **a major organ transplant (eg. heart, lung,** renal, **liver) or hematopoietic stem cell/marrow transplant.**	Clarify subjects with different transplant history need to be excluded
Section 4.2.2 Exclusion Criteria	10. The subject has hypogammaglobulinemia or IgA deficiency (IgA level <10 mg/Dl).	10. The subject has ~~hypogammaglobulinemia or~~ IgA deficiency (IgA level <10 mg/Dl).	Delete hypogammaglobulinemia because it is duplicate with IgA deficiency and exclusion criteria 19.
Section 4.2.2 Exclusion	14. The subject has an abnormality on 12-lead ECG at screening which is	14. The subject has an abnormality on 12-lead ECG at screening which is	Clarification the exclusion

Section	Previous Text	Revised Text	Rationale
Criteria	clinically significant in the opinion of the investigator	clinically significant in the opinion of the investigator**, and which could confound the results of the study. Inclusion may put the subject at undue risk.**	criteria of abnormal ECG.
Section 4.2.2 Exclusion Criteria		**Add :** **21. Received a live vaccine within 30 days of baseline (Day 0).**	Considering the mechanism of action of belimumab, it may impact the immunization, so exclude subjects who received live vaccine within 30 days of baseline.
Section 4.2.2 Exclusion Criteria		**Add :** **22. Have a history of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix.**	To keep consistence among Section3.2.4 Benefit-Risk Assessment and Exclusion Criteria.
Section 4.2.3.1	• Male condom combined with:a female diaphragm, either with or without a vaginal spermicide (foam, gel, cream or suppository).	• Male condom combined with **one of the contraceptive options below:**~~a female diaphragm, either with or without a vaginal spermicide (foam, gel, cream or suppository).~~	Provide detail descriptions on pregnancy requirements

Section	Previous Text	Revised Text	Rationale
		• **Contraceptive subdermal implant** • **Intrauterine device or intrauterine system** • **Combined estrogen and progestogen oral contraceptive Injectable progestogen** • **Contraceptive vaginal ring Percutaneous contraceptive patches**	
5.7.1. Permitted Medications	For subjects with a history of allergies, allergic responses to food, drugs or insects, or a history of urticaria, antihistamine and acetaminophen should be administered prophylactically.	For subjects with a history of allergies, allergic responses to food, drugs or insects, or a history of urticaria, antihistamine and acetaminophen **may be** ~~should be~~ administered prophylactically.	Clarify "should be" is a recommendation; it helps reduce the risk of a reaction for those patients who have a history of allergies.
Section 5.7.2 Prohibited Medications and Non-drug Therapies		**Add:** **From 30 days prior to Day 0** • **Live vaccine**	To keep consistency with the new addition of exclusion criteria 21.

Section	Previous Text	Revised Text	Rationale
Section 6 STUDY ASSESSMENTS AND PROCEDURES	**Paragraph2:** The end time of the infusion will be designated Time 0, and subsequent PK sampling and safety assessments will be performed relative to this time.When several procedures are scheduled at the same nominal time point, PK blood sampling should be given priority.	**Add:** **The time assessment window of the each PK blood sample collection is shown in Table 3**.The end time of the infusion will be designated Time 0, and subsequent PK sampling and safety assessments will be performed relative to this time. **It is essential that the exact time of blood sampling, however, should still be accurately recorded. The safety assessments are recommended to be conducted close to PK sample collection; however,** when several procedures are scheduled at the same nominal time point, PK blood sampling should be given priority. **Add:** **Table 3 Time assessment window of the each PK sample collection**	Add Table 3 to clarify the allowed time-window for PK sample collection.
Section 6 Study assessments and Procedures		**In Table 2, Add:** **Inclusion/Exclusion criteria check at pre-dose on Day 0**	To allow using pulse rate monitoring to replace heart rate monitoring if subject has sinus rhythm which is

Section	Previous Text	Revised Text	Rationale
	Notes for Table 2: 1. Each subject must sign an informed consent form prior to undergoing any Screening assessments. 2. Vital signs include temperature, sitting blood pressure and heart rate. 3. Clinical Laboratory test include hematology, chemistry and urinalysis (including C-reactive protein [CRP] and Erythrocyte Sedimentation Rate on screening). ALT and/or AST elevations of greater than 2.5 x ULN will require additional Hepatitis B assessment, see Section 6.2.1.1 4. HIV antibody, Hepatitis B surface antigen, anti-HBc and Hepatitis C antibody. 5. Pregnancy should be assessed with a blood test at Screening and with a urine test during the treatment period. Pregnancy beyond Day 84 and within 16 weeks after last dose of IP will be assessed with a homekit and subjects can report the results via phone to site. 6. Biomarkers include immunoglobulins B cell subsets (CD20+, CD20+/27+ memory, CD20+/27–naïve, CD20+/69+ activated, CD20+/138+	**In Table 2, update table footnotes:** 1. Each subject must sign an informed consent form prior to undergoing any Screening assessments. **2. <u>Clinical laboratory test at screening visit will be used for inclusion/exclusion criteria check.</u>** 3. Vital signs include temperature, sitting blood pressure and heart rate. **<u>Pulse rate could be used to replace heart rate monitoring if subject has sinus rhythm.</u>** 4. Clinical Laboratory test include hematology, chemistry and urinalysis (including C-reactive protein [CRP] and Erythrocyte Sedimentation Rate on screening). ALT and/or AST elevations of greater than 2.5 x ULN will require additional Hepatitis B assessment, see Section 6.2.1.1. **<u>For pre-dose safety lab monitoring including urine pregnancy test and 12 lead ECG, it's recommended to be done on day 0 or within 48 hours prior to day 0 if site logistic management are limited on day 0 for drug dosing and intensive PK</u>**	matching clinic practice. To exclude subjects who violate inclusion/exclusion criteria before dosing on Day 0. To increase flexibility based on site real situation.

Section	Previous Text	Revised Text	Rationale
	plasmacytoid, CD19+/27BRIGHT/38BRIGHT SLE subset and CD20-/138+ plasma cells). 7. Only immunoglobulins (IgG, IgM and IgA) and auto antibodies (anti-dsDNA, ANA). 8. Includes subject history to be reported on CRF regarding any general signs or symptoms of infection. 9. If a subject prematurely withdraws for any reason, the investigator must make every effort to assess the items specified on discontinuation test.	**sample collection.** 5. HIV antibody, Hepatitis B surface antigen, anti-HBc and Hepatitis C antibody. 6. Pregnancy should be assessed with a blood test at Screening and with a urine test during the treatment period. Pregnancy beyond Day 84 and within 16 weeks after last dose of IP will be assessed with a homekit and subjects can report the results via phone to site.. 7. Biomarkers include immunoglobulins, 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). 8. Only immunoglobulins (IgG, IgM and IgA) and auto antibodies (anti-dsDNA, ANA). 9. Includes subject history to be reported on CRF regarding any general signs or symptoms of infection. **10. The recommended date of**	

Section	Previous Text	Revised Text	Rationale
		<u>"Admission to the Unit" and "Discharge" is only a suggestion. The subject can be admitted to unit from Day -2 to Day 0 and/or discharged on Day 1 based on site flexibility and resource allocation.</u> 11. If a subject prematurely withdraws for any reason, the investigator must make every effort to assess the items specified on discontinuation test.	
Section 6.1.2 Pre-dose examination		**Add:** **<u>Inclusion/Exclusion criteria check</u>**	To exclude subjects who violate inclusion/exclusion criteria before dosing on Day 0.
Section 6.2.1 Liver Chemistry Follow-up Procedures	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.	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, **<u>total IgG.</u>**	Total IgG was added according to the latest global safety requirement.