Sponsor Signatory: **Signature:**   **Date:**

PPD

David Gordon, MBChB
Vice President,
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3/4/15

CLINICAL PROTOCOL HGS1006-C1100
Protocol Amendment: 04
Date: 26 February 2015
EudraCT 2011-004569-33

Amend 01
22Jun12

Amend 02
25Apr13

Amend 03
04Feb14

Amend 04
26Feb15

TITLE OF STUDY:

A Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

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

Confidentiality

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Human Genome Sciences, Inc.   Confidential   Page 2
Clinical Protocol HGS1006-C1100 Amend 04   Belimumab

Revision Chronology for HGS1006-C1100 (BEL115466)

	Date	**Document***
Global	07 March 2012	Original
Global	22 June 2012	Amendment No 01
Local	29 January 2013	Addendum 01 for Sweden
Local DNG2013N160488_01	31 January 2013	Addendum 01 for Ireland
Global DNG2013N167980_00	25 April 2013	Amendment No 02
Global DNG2013N167980_01	04 February 2014	Amendment No 03
Local DNG2014N217970_01	01 October 2014	Local Amendment 01 for France
Local DNG2014N217970_02	03 February 2015	Local Amendment 02 for France
Global DNG2013N167980_02	26 February 2015	Amendment No 04

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

Investigator Agreement

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

Principal Investigator:

_____

Signature   *Date*

_____

Name (please type or print)

_____

Institution

_____

Address

Study Synopsis

Study Number: HGS1006-C1100

Title of the Study:

A Multi-Center, Multinational, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

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Clinical Development Phase: 3

Objectives:

- To evaluate the efficacy of belimumab in the maintenance of remission following a standard induction regimen in subjects with Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA).
- To evaluate the safety of belimumab in subjects with WG or MPA.

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

1. Are at least 18 years of age.
2. Have a clinical diagnosis of Wegener's granulomatosis (WG) or a diagnosis of microscopic polyangiitis (MPA) according to the Chapel Hill criteria (Appendix 1 and Appendix 2).
3. In the 26 weeks prior to randomization (Day 0), had an episode of moderately to severely active WG or MPA requiring treatment under one of the following induction regimens:

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    A single course of rituximab administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
    A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR
    cyclophosphamide 2 mg/kg/day orally plus HDCS OR
    cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.
    [The cyclophosphamide dosing regimens are provided as targets but may be adjusted for older age, obesity, renal insufficiency, leukopenia, or other toxicities as dictated by local practice.]
4. Have documented evidence of either anti-proteinase 3 (anti-PR3) or anti-myeloperoxidase (anti-MPO) prior to Day 0.
5. Have a Birmingham Vasculitis Activity Score (BVAS v.3 [Appendix 3]) of 0 and be receiving ≤ 10 mg/day oral prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart, between 6 and 26 weeks after the first dose of induction therapy (either CYC or RTX, as defined in Section 3.1). A minimum 6 week period should elapse between initiation of induction therapy and randomization.

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6. Subjects receiving non-systemic corticosteroids for reasons other than vasculitis must be on a stable regimen prior to randomization.

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

    Not pregnant or nursing;
    Of non-childbearing potential (ie, women who had a hysterectomy, are postmenopausal which is defined as 12 consecutive months with no menses without an alternative medical cause, have both ovaries surgically removed or have current documented tubal ligation or other permanent sterilization procedure); or
    Of childbearing potential (ie, women with functional ovaries and no documented impairment of oviductal or uterine function that would cause sterility). This category includes women with oligomenorrhoea [even severe], women who are peri-menopausal or have just begun to menstruate. These women must have a negative serum pregnancy test at screening, and agree to 1 of the following:

    o   Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent; or
    o   Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:
        o   Implants of levonorgestrel or etonogestrel;
        o   Injectable progesterone;
        o   Transdermal contraceptive patch
        o   Any intrauterine device (IUD) with a documented failure rate of less than 1% per year;
        o   Oral contraceptives (either combined or progesterone only);
        o   Ethinyl estradiol/Etonogestrel vaginal ring
        o   Double barrier method: Condom and Occlusive cap (diaphragm or cervical/vault caps) with spermidical foam/gel/film/cream/suppository; or
        o   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.

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

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

1. Co-existence of other multisystem autoimmune diseases.

2. Known intolerance or contraindications to azathioprine (AZA); and known intolerance or contraindications to methotrexate where methotrexate is being considered as an alternative to AZA for maintenance therapy.

3. Have received treatment with a B-cell directed therapy (other than rituximab), for example anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], anti-CD40L antibody [BG9588/

IDEC-131], BLyS-receptor fusion protein [BR3], LY2127399, TACI-Fc, or belimumab at any time.

4. Have required 3 or more courses of systemic corticosteroids for concomitant conditions not related to their vasculitis (eg, asthma, atopic dermatitis) within 364 days of Day 0. (Topical or inhaled steroids are permitted.)

5. Have received a non-biologic or biologic investigational agent within 60 days or 5 half-lives of the agent (whichever is longer) of Day 0.

6. Have received a live vaccine within 30 days of Day 0.

7. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to vasculitis (ie, cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious disease) which, in the opinion of the principal investigator, could confound the results of the study or put the subject at undue risk.

8. Have a planned surgical procedure or a history of any other medical disease (eg, cardiopulmonary), laboratory abnormality, or condition (eg, poor venous access) that, in the opinion of the principal investigator, makes the subject unsuitable for the study.

9. 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.

10. Have required management of acute or chronic infections, as follows:

    Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, aspergillosis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
    Hospitalization for treatment of infection within 60 days of Day 0.
    Use of parenteral (intravenous, subcutaneous or intramuscular) antibiotics, antibacterials, antivirals, anti-fungals, or anti-parasitic agents within 60 days of Day 0.

11. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 0.

12. Have a historically positive HIV test or test positive at screening for HIV.   Amend 02 25Apr13

13. Hepatitis B: Serologic evidence of Hepatitis B (HB) infection based on the results of testing for HBsAg, anti-HBc and anti-HBs as follows: Amend 02 25Apr13

    Patients positive for HBsAg are excluded.
    Patients negative for HBsAg and anti-HBc antibody but positive for anti-HBs antibody and with no history of Hepatitis B vaccination are excluded.
    Patients negative for HBsAg but positive for both anti-HBc and anti-HBs antibodies are excluded.
    Patients negative for HBsAg and anti-HBs antibody but positive for anti-HBc antibody are excluded.

14. Hepatitis C: Positive test for Hepatitis C antibody confirmed on a subsequent blood sample by RNA-PCR assay. Subjects who are positive for Hepatitis C antibody and negative when the Hepatitis C RNA-PCR assay is performed on a subsequent sample will be eligible to participate. Subjects who are positive for Hepatitis C antibody and have a positive result for the HCV when the Hepatitis C RNA-PCR assay is performed on the subsequent sample will not be eligible to participate.   Amend 02 25Apr13

15. Have an IgA deficiency (IgA level < 10 mg/dL).

16. Have a Grade 3 or greater laboratory abnormality based on the protocol DMID toxicity scale, unless considered by the investigator to be related to the underlying disease or induction therapy.

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

18. Subjects who have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months and/or any suicidal ideation of type 4 or 5 on the C-SSRS (Refer to Appendix 8 for C-SSRS) in the last 2 months or who in the investigator's opinion, pose a significant suicide risk.

19. Subjects who have abnormal liver function tests defined as follows: 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%). Amend 02
25Apr13

Study Design and Schedule:

This is a multi-center, multi-national, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen. Amend 04
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Subjects enrolled into the trial must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either cyclophosphamide (CYC) or rituximab (ie, induction therapy) in the 6 months leading up to randomization. Subjects treated under the following induction regimens will be eligible for participation in the study: Amend 01
22Jun12

- A single course rituximab (RTX) administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR Amend 01
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- A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR Amend 03
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- Cyclophosphamide 2mg/kg/day orally plus HDCS OR
- Cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

[The cyclophosphamide dosing regimens are provided as targets but may be adjusted for older age, obesity, renal insufficiency, leukopenia, or other toxicities as dictated by local practice.] Amend 01
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For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 0.5-1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ≤ 10 mg/day. As doses for HDCS pulses per the protocol are recommended doses, local Amend 01
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standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.

Subjects who are between 6 and 26 weeks of starting induction therapy, achieve a BVAS v.3 score of 0 (Appendix 4), and are receiving $\leq$ 10 mg/day prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart may be enrolled into the study. A minimum 6 week period should elapse between initiation of induction therapy and randomization. Randomization will be performed on Day 0. A schematic of the study design is shown below.
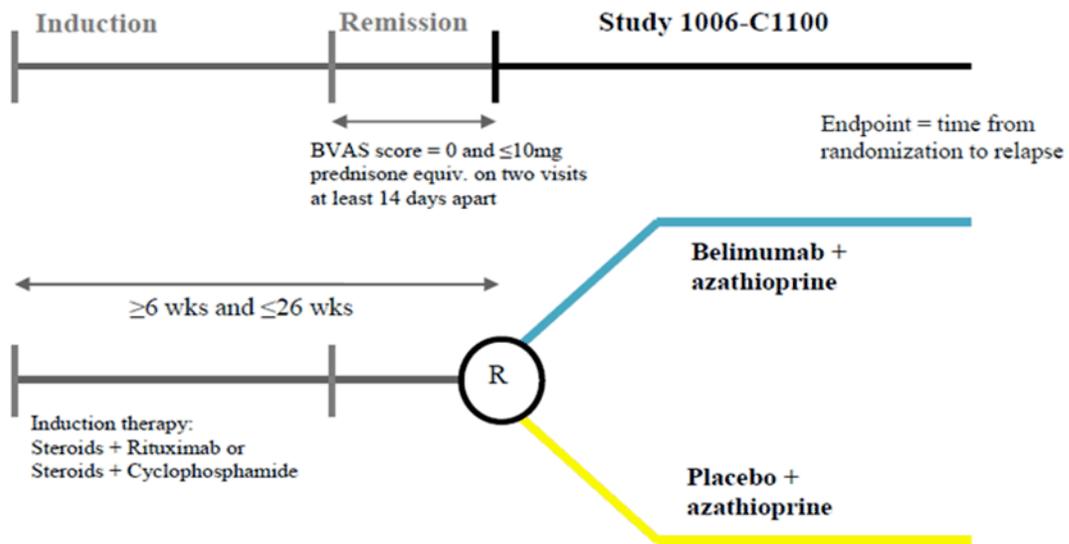
All randomized subjects should be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. Azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine should not be initiated any later than Day 0. Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). Belimumab or placebo will be supplied by the sponsor during this double-blind treatment phase. It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, 28, and every 28 days thereafter.

Initial randomization will be limited to 40 subjects per induction regimen (40 post-RTX induction and 40 post-CYC induction). Once the first 20 patients randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the independent data monitoring committee (DMC), who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with CYC. At all times the sites and sponsor will remain blinded to treatment allocation.

Subjects will receive study agent (belimumab/placebo) plus AZA until the study has completed or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see below). The study will complete, the database will be locked and the primary analysis will be performed when 12 months have elapsed after the last subject is randomized.

Subjects who discontinue study agent prior to relapse/flare (as defined below) are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an attempt will be made to ascertain survival status at 12 months after the first dose of study agent.

Schematic of study design:

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Induction — Remission — Study 1006-C1100

BVAS score = 0 and ≤10mg prednisone equiv. on two visits at least 14 days apart

Endpoint = time from randomization to relapse

≥6 wks and ≤26 wks

Induction therapy:
Steroids + Rituximab or
Steroids + Cyclophosphamide

R

Belimumab + azathioprine

Placebo + azathioprine

Efficacy Endpoints and Analysis:

Primary Efficacy Endpoint:

The primary efficacy endpoint is time from Day 0 to the first relapse, defined as:

- At least 1 major BVAS item (Appendix 4) OR
- A minimum total BVAS score of 6 (Appendix 4) OR
- Receipt of prohibited medications (as defined in Section 5.5.1).

Major Secondary Efficacy Endpoint:

- Time from Day 0 to the first major relapse (defined as experiencing at least 1 major BVAS item, see Appendix 4).

Other efficacy endpoints are described in Section 8.5.4.

Sample Size Considerations:

Approximately 100 subjects will be randomized. The sample size has been determined based on the feasibility of enrolling patients into the study within a reasonable time-frame. The sample size was not based on statistical considerations and the analysis of primary and secondary endpoints will be exploratory in nature. The primary efficacy analysis will be performed after 12 months have elapsed following randomization of the last subject.

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Although the sample size is based on feasibility, the minimal detectable effect has been determined. Assuming an observed relapse rate at 18 months of 20% in the placebo group, a relapse rate of ≤7.0% on belimumab (hazard ratio ≤0.32) would be statistically significant (p<0.05) in a study of 100 subjects (50 per arm).

Analysis of Primary Efficacy Endpoint:

The primary efficacy analysis will compare the time to first relapse from Day 0 between the placebo/azathioprine group and the belimumab/azathioprine combination group using a Cox proportional hazards model, adjusted for ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide). However, the adjustment of induction regimen will be changed to rituximab vs. IV and/or oral cyclophosphamide if the number of events (relapse) is less than 5 in subjects using oral cyclophosphamide or IV cyclophosphamide. For any subject who does not experience a relapse, the time to first relapse will be censored at the time of the subject's last assessment.

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The primary efficacy analysis will be performed after 12 months have elapsed following randomization of the last subject.

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Analysis of Major Secondary Efficacy Endpoints:

The analysis of the major secondary efficacy endpoint will be performed using the same method described for the primary efficacy analysis, but censoring subjects who receive any prohibited medication prior to an observation of any major BVAS item.

Safety Endpoints and Analysis:

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

Adverse events of special interest that will be analyzed in this protocol include: all-cause mortality; serious and/or severe infections; opportunistic infections; infusion reactions including hypersensitivity reactions; malignant neoplasms; selected serious psychiatric events; suicidality assessment (Appendix 8); and immunogenicity.

An independent Data Monitoring Committee (DMC) will review safety data on an ongoing basis until the data are locked and analyzed. The DMC will include at least 3 physicians and a statistician, none of whom are affiliated with the Sponsor. The first DMC reviews will occur after the first 20 subjects per induction regimen (RTX or IV/oral CYC) have been randomized and have had a Week 8 visit. Once the first 20 subjects randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the DMC, who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with IV or oral CYC. The DMC will review the data approximately every 6 months thereafter across both induction regimens. At all times the sites and sponsor will remain blinded to treatment allocation. The DMC will monitor this trial until the data are locked, unblinded, and analyzed for the primary efficacy outcome, after which time monitoring may be assumed by an internal Human Genome Sciences (HGS) committee. Investigators and IRBs/ECs will be notified of the outcome of each DMC meeting.

PK Endpoints and Analysis:

Serum samples will be collected from all randomized subjects who receive a dose of study agent during the study and analyzed to determine serum belimumab concentrations. Serum belimumab concentration data will be used in a population PK analysis, which will be reported separately.

Immunogenicity:

Serum samples for the measurement of anti-belimumab antibodies will be obtained from all subjects before administration of study agent on Day 0, Week 8, Week 24, Week 48 and Exit/8-week Follow-up. Additionally, samples will be obtained from subjects at Weeks 24 and 48 during additional years. For any subject who had a positive antibody response at the 8-week follow-up visit (or last study visit at which immunogenicity was assessed if 8-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum

sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or after completion and/or unblinding of the study, whichever is later.

Biological Markers and Autoantibodies:

Pharmacogenetic sampling (in consenting subjects) will be taken once during the course of this study (see Appendix 9).

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

- Anti-neutrophil cytoplasmic antibody (ANCA: antiPR3, anti-MPO)
- Serum complement (C3, C4)
- Serum immunoglobulin isotypes (IgA, IgM, IgG)
- C-reactive Protein (CRP)
- Erythrocyte sedimentation rate (ESR)
- Urinary protein: urinary creatinine ratio
- BLyS protein (Day 0 only)
- FACS of peripheral lymphocytes

Study Calendar

See Section 6 for a calendar of study visits and assessments.

Table of Contents

List of Tables

List of Abbreviations

AAV	ANCA-associated vasculitis
aCL	anticardiolipin
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ANCA	anti-neutrophil cytoplasmic antibodies
Anti-dsDNA	anti-double-stranded DNA
Anti-MPO	anti- myeloperoxidase
Anti-PR3	anti-proteinase 3
Anti-RNP	anti-ribonucleoprotein
Anti-Sm	anti-Smith antibody (see Sm)
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the serum drug concentration-time curve
AZA	azathioprine
BAFF	B Cell Activating Factor belonging to the TNF Ligand Family
BILAG	British Isles Lupus Assessment Group of SLE Clinics
BLyS	B lymphocyte Stimulator
BR3	BLyS-receptor fusion protein
BUN	blood urea nitrogen
BVAS	Birmingham Vasculitis Activity Score
℃	degrees Celsius
C3	Complement Factor 3
C4	Complement Factor 4
C-ANCA	Cytoplasmic antineutrophil cytoplasmic antibodies
CHCC	Chapel Hill consensus Conference
Chem	chemistry
Cl_{cr}	creatinine clearance
Coag	Coagulation
CPK	creatine phosphokinase
CRF	case report form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSS	Churg-Strauss Syndrome
C-SSRS	Columbia-Suicide Severity Rating Scale
CYC	cyclophosphamide
dL	deciliter
DMC	Data Monitoring Committee
DMID	Division of Microbiology & Infectious Diseases
DNA	deoxyribonucleic acid
dsDNA	double stranded DNA
DSM	Diagnostic and Statistical Manual

ECG	electrocardiogram
ECL	electrochemiluminescence
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
ESR	erythrocyte sedimentation rate
EU	Europe
FACS	florescence activated cell sorting
Fc	immunoglobulin constant region (fragment crystallizable)
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GPA	Granulomatosis with polyangiitis
HB	hepatitis B
HBsAg	hepatitis B surface antigen
HBc	hepatitis B core
HDCS	high dose corticosteroids
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HGS	Human Genome Sciences, Inc.
HIV	human immunodeficiency virus
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IM	intramuscular
INR	International Normalized Ratio
INN	international nonproprietary Name
IRB	Institutional Review Board
ITT	intention to treat
IUD	intrauterine device
IV	intravenous
IVIG	intravenous immunoglobulin
IWRS	Interactive Web Response System
kDa	kilodalton
kg	kilogram
LDH	lactate dehydrogenase
m^2	meters squared
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MTX	methotrexate

n	number
μg	microgram
mg	milligram
mL	milliliter
OD	optical density
PAN	polyarteritis nodosa
P-ANCA	perinuclear antineutrophil cytoplasmic antibodies
PGx	pharmacogenetics
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PR3	proteinase 3
PSE	protocol specified events
PSRHQ	possible suicidality related history questionnaire
PSRQ	possible suicidality related questionnaire
PT	prothrombin time
PTT	partial thromboplastin time
RA	rheumatoid arthritis
RBC	red blood cell
RF	rheumatoid factor
RTX	rituximab
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SLE	Systemic lupus erythematosus
SOC	System Organ Class
SRI	SLE responder index
SWFI	sterile water for injection
$t_{1/2,term}$	terminal half-life
TACI	transmembrane activator and calcium-modulator and cyclophilin ligand interactor
TEN	toxic epidermal necrolysis
TNFSF13B	Tumor Necorsis Factor Superfamily Member 13 B
TPMT	thiopurine methyltransferase
ULN	upper limits of normal
USA	United States of America
USAN	United States Adopted Name
VDI	Vasculitis Damage Index
WBC	white blood cell
WG	Wegener's Granulmatosis (Granulomatosis with polyangiitis)

1 Background

1.1 Disease Background

The systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies including infective and drug-induced causes and can be either primary or secondary to other diseases such as SLE. A subset of the primary small vessel vasculitides: Wegener's granulomatosis (also commonly referred to as granulomatosis with polyangiitis [GPA]), microscopic polyangiitis and Churg-Strauss syndrome (CSS), are characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) (Jennette and Falk, 1997). ANCA-associated vasculitides (AAV) are multisystem diseases with a broad range of manifestations from cutaneous ulcers, scleritis, pericarditis to life-threatening manifestations such as lung hemorrhage and renal failure. All 3 forms of AAV share the characteristic of systemic necrotizing vasculitis; WG and CSS are further characterized by granuloma formation. Historically, ANCA have been classified on the basis of their staining patterns in immunofluoresence assays as either cytoplasmic (C-ANCA) or perinuclear (P-ANCA). It is now recognized that in AAV, C-ANCA is usually directed against proteinase 3 (PR3), and P-ANCA is generally directed against myeloperoxidase (MPO), both of which are enzymes that are abundant in the granules of neutrophils (Jennette and Falk, 1997; Merkel et al, 1997). Anti-PR3 antibodies are generally associated with WG, while anti-MPO autoantibodies are more common in MPA and CSS. Anti-PR3 antibodies are associated with increased morbidity and mortality compared to anti-MPO (Hogan et al, 1996; Franssen et al, 1998). The most widely used classification criteria for diagnosing the 3 types of AAV are those published by the American College of Rheumatology (ACR) for WG and CSS (Leavitt et al, 1990 and Masi et al, 1990, respectively), and that published by the Chapel Hill Consensus Conference (CHCC) for MPA (Jennette et al, 1994; Jennette et al, 2013). Of note, none of these diagnostic criteria incorporate the measurement of ANCA. The Chapel Hill criteria for WG can be found in Appendix 1 and for MPA in Appendix 2.

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Amend 02 25Apr13

The precise epidemiology of these diseases is uncertain as early studies did not utilize the same classification criteria as later ones (Koldingsnes and Nossent, 2008; Watts et al, 2007; Mahr, 2009). In the case of MPA, in particular, epidemiological studies are confounded by its original inclusion as a form of polyarteritis nodosa (PAN). Utilising the ACR or CHCC criteria, prevalence rates range from 5-16/100000 for WG, 2.5-9.4/100000 for MPA, and 0.4-1.4/100000 for CSS making the latter the least prevalent of the three by some margin (Koldingsnes and Nossent, 2008). In the US, the prevalence rates of WG range from 2.6-9/100000 (Zeft et al, 2005; Mahr et al, 2006). AAV are extremely rare in childhood with peak age of onset in those aged 65 to 74 years (Ntatsaki et al, 2010), with other small vessel vasculitides being the major concern in childhood (Brogan et al, 2010).

Amend 02 25Apr13

Current therapy is usually determined by severity of the disease, with more severe forms warranting more aggressive approaches. These usually involve an initial remission induction regimen of high dose corticosteroid administered with either cyclophosphamide or rituximab followed by a remission maintenance period usually with azathioprine (Stone et al, 2010; Bosch et al, 2007; Jayne et al, 2003). Minor manifestations are usually treated with low dose corticosteroid administered with either azathioprine or methotrexate (Belmont, 2006). Even

with recent treatment advances the morbidity and mortality of patients with AAV remains unacceptably high (Drooger et al, 2009).

The Birmingham Vasculitis Activity Score (BVAS) was developed and validated as a tool to measure disease activity (Luqmani et al, 1994). It has been modified to form the BVAS/WG (Stone et al, 2001) and updated most recently with the validation of version 3 of the instrument, also known as BVAS 2003 (Mukhtyar et al, 2008, Appendix 3). In its current form it is a list of 56 items which are considered to be manifestations of vasculitis. A weighted numerical score is attached to each item to reflect the importance of each manifestation. The items are grouped by organ systems, and each organ system has a maximum or 'ceiling' score to reflect the relative importance of the organ system (Mukhtyar et al, 2008). The tool also makes a distinction between new or worsening disease and persistent disease with new or worsening attracting higher scores.

1.2   Study Agent Background

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

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

1.3   Clinical Experience

1.3.1   Belimumab Administered Intravenously

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

Phase 3 studies of belimumab in SLE were completed in 2009 and 2010 and formed the basis of IV belimumab in the US, Canada and EU. The Phase 3 trials included 1,684 subjects where belimumab 10 mg/kg plus standard therapy demonstrated superiority over placebo plus standard therapy in reduction in disease activity as measured by the SLE responder index (SRI) with an acceptable safety profile. The primary safety population supporting approval also included data from a Phase 2 study in 449 subjects with SLE. Evidence of benefit in other clinical measures such as reductions in disease activity as measured by SELENA SLEDAI, severe flare, and reduced steroid use was also observed. Treatment with belimumab plus standard of care was generally well tolerated, with rates of adverse events (AEs), severe AEs, serious AEs, AEs leading to discontinuation and serious/severe infections generally comparable to the rates observed in the placebo plus standard of care group. Mortality rates in the controlled clinical trials were low, although numerically higher in the belimumab groups:

0.4% and 0.8% in the placebo and belimumab groups, respectively. Causes of death were as expected in an SLE population with active disease receiving a wide range of standard therapies, such as steroids and immunosuppressants, and included infection, cardiovascular disease, and suicide. Serious infections were observed in 5.2% and 6.0% of subjects receiving placebo and belimumab, respectively. The rate of malignancy (excluding non-melanoma skin cancer) was the same between the placebo and belimumab groups at 0.4%; however as with other immunomodulating agents, the mechanism of action of belimumab could increase the risk for the development of malignancies. Hypersensitivity and infusion reactions were observed. Anaphylaxis was also observed, though rare (< 1%). Depression-related events, common in patients with SLE, were observed more frequently with belimumab than with placebo; it is unknown if belimumab treatment is associated with an increased risk for these events. The most commonly-reported adverse reactions, occurring in ≥ 5% of subjects in clinical trials were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis.

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

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

A benefit-risk evaluation of belimumab in the context of the present study is provided in Appendix 12 of this protocol.

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1.4   Rationale for the Study

Studies in subjects with WG and MPA have shown the need for more effective treatment for the maintenance of remission, with relapse rates with these 2 diseases ranging from 15% at 18 months (Jayne et al, 2003) to 38% at 3 years (Hiemstra et al, 2010) on azathioprine − the most effective of current therapies (Jayne et al, 2003; Pagnoux et al, 2008; Hiemstra et al, 2010).

The presence of ANCA autoantibodies in AAV implicates B cells in the pathogenesis of AAV. Further supporting a role for B cells is the fact that activated B cells are present in greater numbers in GPA subjects compared with healthy persons (Popa et al, 1999). Additionally, elevated levels of BLyS, a B cell survival factor, are found in subjects with AAV (Krumbholz et al, 2005; Nagai et al, 2011; Schneeweis et al, 2010). Together, these provide a strong pharmacologic rationale for the use of belimumab to treat AAV, since belimumab has been shown in SLE to reduce both B cells and autoantibody levels.

The fact that rituximab, a biologic therapy that targets B cells by binding to the B cell surface antigen CD20 (Dass et al, 2008; Wang et al 2008), recently showed success in inducing

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remission in AAV (Stone et al, 2010) and was granted approval for the treatment of WG and MPA supports the rationale that belimumab, which down regulates B cells by targeting BLyS, may be useful in the treatment of this disease. Finally, limited data from the small (n = 111) subset of subjects in the Phase 3 trials of SLE who had vasculitic symptoms as part of their SLE (as assessed by the SELENA SLEDAI) showed that more subjects in the belimumab plus standard of care treatment arms had resolution of their vasculitic symptoms at Week 52 compared with subjects receiving placebo plus standard of care. Specifically, 19/36 (52.8%) and 28/38 (73.7%) of subjects in the belimumab 1 mg/kg and 10 mg/kg dose groups, respectively, had resolution of vasculitic activity at Week 52 compared with 15/37 (40.5%) of placebo subjects. Taken together, these data support the evaluation of belimumab in AAV.

2 Study Objectives

2.1 Primary Objective

1. To evaluate the efficacy of belimumab in the maintenance of remission following a standard induction regimen in subjects with Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA).
2. To evaluate the safety of belimumab in subjects with WG or MPA.

3 Study Design

3.1 Basic Design Characteristics

This is a multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen. Subjects enrolled into the trial must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either cyclophosphamide (CYC) or rituximab (ie, induction therapy) in the 6 months leading up to randomization. Subjects treated under the following induction regimens will be eligible for participation in the study: *(Amend 04 26Feb15)* *(Amend 01 22Jun12)*

- A single course rituximab (RTX) administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR *(Amend 01 22Jun12)*
- A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval plus HSCS OR *(Amend 03 04Feb14)*
- Cyclophosphamide 2mg/kg/day orally plus HDCS OR
- Cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

[The cyclophosphamide dosing regimens are provided as targets but may be adjusted for older age, obesity, renal insufficiency, leukopenia, or other toxicities as dictated by local practice.] *(Amend 01 22Jun12)* *(Amend 03 04Feb14)*

For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 0.5-1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ≤ 10 mg/day. As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.

Subjects who between 6 and 26 weeks of starting induction therapy, achieve a BVAS v.3 score of 0 (Appendix 4) and are receiving ≤ 10 mg/day oral prednisone (or equivalent) on 2 consecutive visits at least 14 days apart may be enrolled into the study. A minimum 6 week period should elapse between initiation of induction therapy and randomization. Randomization will be performed on Day 0. A schematic of the study design is shown in Figure 1.

Figure 1 Schematic of study design

All randomized subjects should be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. Azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine should not be initiated any later than Day 0. Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to also receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously over 1 hour. The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV

cyclophosphamide vs. oral cyclophosphamide vs. rituximab). Belimumab or placebo will be supplied by the sponsor during this double-blind treatment phase. It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent will be administered at Day 0, 14, 28 and every 28 days thereafter.

Initial randomization will be limited to 40 subjects per induction regimen (40 post-RTX induction and 40 post-CYC induction). Once the first 20 patients randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the independent data monitoring committee (DMC), who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with CYC. At all times the sites and sponsor will remain blinded to treatment allocation.

Subjects will receive study agent (belimumab/placebo) plus AZA until the study has completed or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1). The study will complete, the database will be locked, and the primary analysis will be performed when 12 months have elapsed after the last subject is randomized.

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an attempt will be made to ascertain survival status at 12 months after the first dose of study agent.

4 Inclusion and Exclusion Criteria

4.1 Inclusion Criteria

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

1. Are at least 18 years of age.
2. Have a clinical diagnosis of Wegener's granulomatosis or a diagnosis of microscopic polyangiitis (MPA) according to the Chapel Hill criteria (Appendix 1 and Appendix 2).
3. In the 26 weeks prior to Day 0, had an episode of moderate to severely active WG or MPA requiring treatment under one of the following induction regimens:

    A single course of rituximab administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
    A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR
    cyclophosphamide 2 mg/kg/day orally plus HDCS OR
    cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

4. Have documented evidence of either anti-PR3 or anti-MPO prior to Day 0.

5. Have a Birmingham Vasculitis Activity Score (BVAS v.3 [Appendix 3]) of 0 and be receiving ≤ 10 mg/day oral prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart, between 6 and 26 weeks after the first dose of induction therapy (either CYC or RTX, as defined in Section 3.1). A minimum 6 week period should elapse between initiation of induction therapy and randomization. Amend 03
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6. Subjects receiving non-systemic corticosteroids for reasons other than vasculitis must be on a stable regimen prior to randomization.

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

   Not pregnant or nursing;
   Of non-childbearing potential (ie, women who had a hysterectomy, are postmenopausal which is defined as 12 consecutive months with no menses without an alternative medical cause, have both ovaries surgically removed or have current documented tubal ligation or other permanent sterilization procedure); or Amend 02
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   Of childbearing potential (ie, women with functional ovaries and no documented impairment of oviductal or uterine function that would cause sterility). This category includes women with oligomenorrhoea [even severe], women who are perimenopausal or have just begun to menstruate. These women must have a negative serum pregnancy test at screening, and agree to 1 of the following:
   - Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent; or
   - Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:
     - Implants of levonorgestrel or etonogestrel;
     - Injectable progesterone;
     - Transdermal contraceptive patch
     - Any intrauterine device (IUD) with a documented failure rate of less than 1% per year;
     - Oral contraceptives (either combined or progesterone only);
     - Ethinyl estradiol/Etonogestrel vaginal ring;
     - Double barrier method: Condom and Occlusive cap (diaphragm or cervical/vault caps) with spermidical foam/gel/film/cream/suppository; or
     - 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.

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

4.2   Exclusion Criteria

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

1. Co-existence of other multisystem autoimmune diseases.

2. Known intolerance or contraindications to azathioprine (AZA); and known intolerance or contraindications to methotrexate where methotrexate is being considered as an alternative to AZA for maintenance therapy.

3. Have received treatment with a B-cell directed therapy (other than rituximab), for example anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], antiCD40L antibody [BG9588/ IDEC-131], BLyS-receptor fusion protein [BR3], LY2127399, TACI-Fc, or belimumab at any time.

4. Have required 3 or more courses of systemic corticosteroids for concomitant conditions not related to their vasculitis (eg, asthma, atopic dermatitis) within 364 days of Day 0. (Topical or inhaled steroids are permitted.)

5. Have received a non-biologic or biologic investigational agent within 60 days or 5 half-lives of the agent (whichever is the longer) of Day 0.

6. Have received a live vaccine within 30 days of Day 0.

7. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to vasculitis (ie, cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious disease) which, in the opinion of the principal investigator, could confound the results of the study or put the subject at undue risk.

8. Have a planned surgical procedure or a history of any other medical disease (eg, cardiopulmonary), laboratory abnormality, or condition (eg, poor venous access) that, in the opinion of the principal investigator, makes the subject unsuitable for the study.

9. 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.

10. Have required management of acute or chronic infections, as follows:

    Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, aspergillosis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
    Hospitalization for treatment of infection within 60 days of Day 0.
    Use of parenteral (IV, SC or IM) antibiotics, antibacterials, antivirals, anti-fungals, or anti-parasitic agents within 60 days of Day 0.

11. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 0.

12. Have a historically positive HIV test or test positive at screening for HIV.

13. Hepatitis B: Serologic evidence of Hepatitis B (HB) infection based on the results of testing for HBsAg, anti-HBc and anti-HBs as follows:

Patients positive for HBsAg are excluded.

Patients negative for HBsAg and anti-HBc antibody but positive for anti-HBs antibody and with no history of Hepatitis B vaccination are excluded.

Patients negative for HBsAg but positive for both anti-HBc and anti-HBs antibodies are excluded.

Patients negative for HBsAg and anti-HBs antibody but positive for anti-HBc antibody are excluded.

14. Hepatitis C: Positive test for Hepatitis C antibody confirmed on a subsequent blood sample by RNA PCR assay. Subjects who are positive for Hepatitis C antibody and negative when the Hepatitis C RNA-PCR assay is performed on a subsequent sample will be eligible to participate. Subjects who are positive for Hepatitis C antibody and have a positive result for the HCV when the Hepatitis C RNA-PCR assay is performed on the subsequent sample will not be eligible to participate.

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15. Have an IgA deficiency (IgA level < 10 mg/dL).

16. Have a Grade 3 or greater laboratory abnormality based on the protocol DMID toxicity scale, unless considered by the investigator to be related to the underlying disease or induction therapy.

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

18. Subjects who have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months and/or any suicidal ideation of type 4 or 5 on the C-SSRS (Refer to Appendix 8 for C-SSRS) in the last 2 months or who in the investigator's judgment, pose a significant suicide risk.

19. Subjects who have abnormal liver function tests defined as follows: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\geq$ 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%).

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5 Study Treatment Regimen

5.1 Study Agent Name and Formulation

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

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

Belimumab drug product is provided as a sterile, lyophilized product in a 20 mL vial. Upon reconstitution with 4.8 mL sterile water for injection (SWFI), each vial will contain 80 mg/mL belimumab in 0.16 mg/mL citric acid, 2.7 mg/mL sodium citrate, 80 mg/mL sucrose, 0.4 mg/mL polysorbate 80, pH 6.5. Each vial is single use.

The placebo control is prepared as a sterile, lyophilized product in a 20 mL vial. Placebo is reconstituted with 4.8 mL SWFI. Upon reconstitution with 4.8 mL sterile water for injection (SWFI), each vial will contain 0.16 mg/mL citric acid, 2.7 mg/mL sodium citrate, 80 mg/mL sucrose, 0.4 mg/mL polysorbate 80, pH 6.5. Each placebo vial is single use.

5.2   Packaging, Labeling, Preparation, and Storage

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

Placebo control will be supplied in a 20 mL vial.

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

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

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

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

The calculated dose of study agent to be administered to the subject is determined in milligrams (mg) by the assigned treatment group and the subject's body weight in kilograms (kg).

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

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

Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

Study agent inventory/accountability forms will be examined and reconciled by the Sponsor or designee. At the end of the study, all used and unused study agent must be accounted for on a study agent accountability form.

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

5.3   Dose, Route of Administration, and Schedule

The treatment groups include one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving azathioprine (as described in Section 5.5.3). Belimumab/placebo will be administered intravenously over 1 hour. The intent of this instruction is to prevent more rapid infusion of belimumab which may result in a higher incidence of infusion reactions. Infusion time need <u>not</u> be exactly one hour as it is often difficult to so precisely adjust infusion times and there may be clinical reasons for infusions lasting longer than one hour. Therefore, the instruction should be interpreted as infusion over <u>at least</u> one hour. The target infusion time should still be approximately one hour assuming no other issues intervene. Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days thereafter.

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

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

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase. 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. Beyond the first 2 infusions, subjects should be monitored during and for an appropriate period of time after infusion according to study sites' guidelines or standard operating procedure for IV infusions.

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

5.4   Alteration of Dose/Schedule Due to Toxicity

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

If a subject experiences a clinically significant AE that the investigator believes may be definitely, possibly or probably related to belimumab/placebo and could potentially be exacerbated by the next dose, the investigator may delay the dose by up to 2 weeks or withhold 1 dose. If a similar concern is present after 2 weeks, the investigator should contact the medical monitor to determine whether treatment should be discontinued.

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

5.5   Concurrent Medications

5.5.1 Prohibited Medications and Therapies that Result in Treatment Failure

Subjects who start prohibited medication or therapies at any time during the double-blind phase will be considered as having relapsed as of the time of receipt of the prohibited medication, and treatment with study agent will be discontinued. However, the subject will continue to be followed for survival through at least 12 months after randomization. The following medications and therapies are prohibited during the study:

- Other immunomodulatory investigational agents (biologic or non-biologic);
- Rituximab;
- Cyclophosphamide;
- Other immunosuppressive agents (eg, cyclosporine) with the exception of methotrexate for AZA intolerance described in Section 5.5.3;
- Corticosteroids for vasculitis:

doses > 20 mg/day prednisone (or equivalent), or
IV corticosteroid pulses at any dose;
Note: Doses of prednisone up to a maximum of 20 mg/day (or equivalent) for vasculitis,
for a maximum of 1 week, are only allowable within the first 2 months of the double-blind
treatment period.

- Corticosteroids for reasons other than vasculitis:
at an average daily dose of > 20 mg/day prednisone (or equivalent) for > 14 days where
the average daily dose is calculated as the sum of the dose over 7 consecutive days divided
by 7, or
IV corticosteroid pulses > 125 mg prednisone (or equivalent)
Note: Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or IV corticosteroid
pulses ≤ 125 mg prednisone (or equivalent) for reasons other than vasculitis cannot be
given more than once in any 365 day period (See also Section 5.5.3).

- Plasmapharesis.

5.5.2 Other Prohibited Medications and Therapies

Due to the mechanism of action of belimumab, it is possible that response to vaccination may
be impaired. Live vaccines should not be given for 30 days before or concurrently with
belimumab/placebo infusions.

Other investigational agents are not permitted.

5.5.3 Allowable Medications

The use of stable baseline dose regimens of corticosteroids (≤ 10 mg/day prednisone or
equivalent) is permitted over the course of the trial. Doses of corticosteroid up to a maximum
of 20 mg/day of prednisone (or equivalent), for vasculitis, are permitted for a maximum of
1 week within the first 2 months of the double-blind treatment period. At other times, subjects
are restricted to ≤ 10 mg/day prednisone or equivalent. It is expected that this dose may be
tapered as clinically appropriate. Inhaled corticosteroids for asthma, or topical corticosteroids
for atopic dermatitis are also permitted. Doses of prednisone (or equivalent) > 20mg/day for ≤
14 days or an IV corticosteroid pulse up to 125 mg prednisone (or equivalent) are permitted
for reasons other than vasculitis (eg. acute allergic reaction), but a subject cannot receive more
than 1 such corticosteroid regimen in any 365 day period (See also Section 5.5.1).

5.5.3.1 Azathioprine and Methotrexate

The target dose of azathioprine is 2 mg/kg/day (not to exceed 200 mg/day). For the
maintenance of remission azathioprine may be initiated as soon as it is clinically indicated
following administration of induction therapy. Azathioprine must not be initiated any later
than Day 0. Azathioprine should be started at a dose of 50 mg/day and increased by no more
than 50 mg/day every week until the target dose is achieved.

Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia,
AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction,
characterized by severe nausea and vomiting, following initiation of azathioprine will be

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permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. These subjects will be included in the primary analysis.

For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset. This should be discussed with the medical monitor. Methotrexate would not be recommended for those subjects with significantly impaired renal function.

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The appropriate local prescribing information (eg, dose adjustments, contraindications, hematological and biochemical monitoring, pregnancy, contraception, etc.) for azathioprine or methotrexate (MTX) (as applicable), should be followed prior to and during treatment.

In the extension phase of the trial, the dose of AZA/MTX can be decreased or discontinued based on the discretion of the investigator.

6 Study Procedures

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

Subjects participating in the pharmacogenetics (PGx) research portion of the protocol (Appendix 9) must sign the PGx informed consent prior to any PGx samples being drawn from the subject.

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

6.1 Screening Procedures (Day -60 to Day 0)

The following assessments are required at screening and must be within 60 days prior to or on Day 0:

- Demographics.
- Medical history.
- Lifetime cyclophosphamide exposure.
- Complete physical examination, including height, weight and vital signs.
- Document induction regimen and confirm successful induction of remission for WG or MPA vasculitis.
- Document positive history for either anti-PR3 or anti-MPO.

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- Obtain historical biopsy information for documentation of vasculitis diagnosis as available.
- Confirm subject meets study entry criteria.
- Blood samples for: (see Appendix 6 – Laboratory Tests)
  - Hematology
  - Modified Chem20 (non-fasting)
  - Serum pregnancy test – for all women with an intact uterus, unless exempted from pregnancy testing (ie, of non-childbearing potential – women who had a hysterectomy, are post-menopausal which is defined as 1 year without menses, have both ovaries surgically removed or have current documented tubal ligation or other permanent sterilization procedure)
  - HIV antibody testing, serologic investigations for Hepatitis B (HB) infection (HBsAg, anti-HBc, and anti-HBs), and Hepatitis C antibody testing ± confirmatory HCV RNA-PCR testing   Amend 02
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  - Biological markers (Complement C3, C4)
  - Serum Immunoglobulin isotypes (IgG, IgM, IgA)
  - C-reactive Protein (CRP)
  - Erythrocyte sedimentation rate (ESR)
  - Autoantibodies (ANCA: anti-PR3, anti-MPO)
- Urine Sample for:
  - Routine urinalysis
  - Spot urine for Urinary protein: urinary creatinine
- Suicidality Assessment using the Columbia Suicidality-Severity Rating Scale (C-SSRS) Screening assessment form (see Appendix 8).

6.2   Study Enrollment Procedures

Subjects who have undergone all screening procedures and have met the entry criteria will be enrolled into the study and assigned to treatment by Interactive Web Response System (IWRS). Randomization will be performed on Day 0. Azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine must not be initiated any later than Day 0. Female subjects who require pregnancy testing must have a negative urine pregnancy test done on Day 0, prior to randomization. Subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups (belimumab + AZA or placebo + AZA).   Amend 03
04Feb14

6.3   Double-Blind Treatment Phase

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

At baseline (Day 0), the subject will be randomized and receive the first dose of study agent. Visits to the study site will occur on Day 14, Day 28, and approximately every 28 days (calculated from the Day 0 dose) thereafter. All efforts should be made to retain subjects on schedule, based on the date of their Day 0 dose. Subjects should remain under clinical

supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.

Subjects who have not experienced a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1) will remain on double-blind treatment with study agent until the study has completed. The study will complete and the primary efficacy analysis will be performed when 12 months have elapsed following randomization of the last subject.

<div style="float:right">Amend 04
26Feb15</div>

Subjects will return for an Exit visit (approximately 4 weeks after the last dose of study agent), and a follow-up visit (approximately 8 weeks after the last dose of study agent).

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Table 6-1   Double-blind Treatment Phase Year One

Study Visit	Screening -60 days	Day 0	Week 2 ± 3 days	Week 4 ± 3 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 16 ± 7 days	Week 20 ± 7 days	Week 24 ± 7 days	Week 28 ± 7 days	Week 32 ± 7 days	Week 36 ± 7 days	Week 40 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	Exit[11]	8 Week Follow Up[13]	Un-scheduled
Written Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eligibility Criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Document Successful Induction Regimen	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Obtain Historical Biopsy Report (if available)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Randomization	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clinical Assessments																		
Complete Physical Exam[1]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Symptom Driven Physical Exam	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Weight	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Vital Signs[15,16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
12-lead ECG[16]	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CSSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Record Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess/Record Adverse Events[3]	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[12]	X	X
BVAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
VDI	X	X	-	-	-	X	-	-	X	-	-	X	-	-	X	X	-	-

Table 6-1   Double-blind Treatment Phase Year One

Study Visit	Screening -60 days	Day 0	Week 2 ± 3 days	Week 4 ± 3 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 16 ± 7 days	Week 20 ± 7 days	Week 24 ± 7 days	Week 28 ± 7 days	Week 32 ± 7 days	Week 36 ± 7 days	Week 40 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	Exit[11]	8 Week Follow Up[13]	Un-scheduled
Laboratory Assessments																		
Serum Beta hCG	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV, Hepatitis B, C[17]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology & Modified Chem-20 (non fasting)[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[14]
Coagulation – PT/aPTT and INR	X	X	-	-	X	-	-	-	X	-	-	-	-	-	X	X	-	-
Routine Urinalysis	X	-	-	-	-	X	-	-	X	-	-	X	-	-	X	X	-	-
Urine Pregnancy Test[5]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Urinary protein: urinary creatinine and creatinine clearance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X[14]
Pharmacokinetic Sampling (pre/post Belimumab dose)	-	X Pre	X Post (0-4 hrs)	-	X Pre	-	-	-	X Post (0-4 hrs)	-	-	-	-	-	X Pre	X	X	-
Pharmacogenetic Sampling[6]	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Immunogenicity (anti-belimumab antibodies)[7]	-	X	-	-	X	-	-	-	X	-	-	-	-	-	X	X	X	-
BLyS Protein	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-			-
T cells/B cell subset	-	X	-	X	X	X	-	-	X	-	-	X	-	-	X	X	X	-
C3/C4 and ANCA	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum IgG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Serum IgA & IgM	X	X	-	-	-	X	-	-	X	-	-	X	-	-	X	X	X	
CRP & ESR	X	X	-	-	-	X	-	-	X	-	-	X	-	-	X	X	X	
Protocol Treatments																		
Study agent (Belimumab/Placebo)[8, 9,]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-
AZA administration[10]	X	X	← Throughout the Study →													-	-	-

Footnotes on next page:

Table 6-1 **Footnotes:**

1. Complete physical examination, including height and weight.

2. Any SAEs occurring prior to the start of study agent administration and assessed as related to study participation (eg, protocol-mandated procedures, invasive tests) will be recorded on the SAE worksheet and reported as described in Section 7.2 from the time a subject consents to participate in the study.

3. All adverse events (AEs) and serious adverse events (SAEs) that are identified from the start of study agent administration (Day 0) through 8 weeks following administration of the last dose of study agent should be recorded on the Adverse Event Case Report Form (AE eCRF). SAEs that occur after the 8 week follow-up period that are assessed by the investigator as definitely, possibly or probably related to study agent must be reported to the Drug Safety designee on the SAE worksheet. (Post study SAEs will not be documented on the AE eCRF.)

4. Refer to Appendix 6 for laboratory assessments to be completed.

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

6. In consenting subjects only (Appendix 9).

7. Immunogenicity samples are collected pre-dose at all time points. For any subject who had a positive antibody response at the 8-week follow-up visit (or last study visit at which immunogenicity was assessed if 8-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or after completion and/or unblinding of the study, whichever is later.

8. Subjects who discontinue treatment with study agent (belimumab/placebo) will continue to be followed per this calendar schedule until relapse as defined in Section 8.5.1.

9. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 study agent infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.

10. Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1mg/kg/day. If the patient continues to experience the toxicities described above a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset following discussion with the medical monitor.

11. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 4 weeks after the last dose of study agent). The Exit Visit should be completed for subjects who discontinue the double blind treatment phase early or when subjects have completed the double-blind treatment phase. Subjects who discontinue treatment but have not relapsed will remain on the double blind study visit schedule.

12. In subjects who discontinue study agent all AEs and SAEs will be reported on the AE eCRF through 8 weeks following administration of the last dose of study agent. After this time, all SAEs, regardless of relationship to study drug, will be collected until relapse or the study is analysed for the primary endpoint, whichever occurs first.

13. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent.

14. Hematology and Modified Chem 20, Urinary protein, urinary creatinine and creatinine clearance are not mandatory at Unscheduled Visits and should be obtained only when determined to be clinically indicated by the Principal Investigator.

15. Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate.

16. Complete prior to dosing.

17. HIV, Hepatitis B surface antigen, anti-HBc, anti-HBs and hepatitis C antibody (if hepatitis C antibody positive, HCV RNA-PCR assay will be performed on a subsequent blood sample to confirm the results).

Amend 02
22Apr13

Amend 03
04Feb14

Amend 04
26Feb15

Amend 01
22Jun12

Amend 02
25Apr13

Table 6-2   Double-blind Treatment Phase Additional Years

Study Visit	Week 4 ± 7 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 16 ± 7 days	Week 20 ± 7 days	Week 24 ± 7 days	Week 28 ± 7 days	Week 32 ± 7 days	Week 36 ± 7 days	Week 40 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	Exit[7]	8 Week Follow Up[9]	Un-scheduled
Clinical Assessments															
Symptom Driven Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Vital Signs[11,12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Record Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess/Record Adverse Events[1]	X	X	X	X	X	X	X	X	X	X	X	X	X[8]	X	X
BVAS	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
VDI	-	-	X	-	-	X	-	-	X	-	-	X	X	-	-
Laboratory Assessments															
Hematology & Modified Chem-20 (non fasting)[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]
Coagulation – PT/aPTT and INR	-	-	-	-	-	X	-	-	-	-	-	X	X	-	-
Routine Urinalysis	-	-	X	-	-	X	-	-	X	-	-	X	-	-	-
Urine Pregnancy Test[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Urinary protein: urinary creatinine and creatinine clearance	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X[10]
Pharmacokinetic Sampling (pre or post Belimumab dose)	-	-	-	-	-	X Pre	-	-	-	-	-	X Pre	X	X	-
Immunogenicity (anti- belimumab antibodies)[4]	-	-	-	-	-	X	-	-	-	-	-	X	X	X	-
T cells/B cells	X	-	-	-	-	X	-	-	-	-	-	X	X	X	-
C3/C4 and ANCA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Serum IgG	-	-	X	-	-	X	-	-	X	-	-	X	X	X	-
Serum IgA & IgM	-	-	X	-	-	X	-	-	-	-	-	-	X	X	-
CRP & ESR	-	-	X	-	-	X	-	-	-	-	-	-	X	X	-

Amend 02 25Apr13

Amend 01 22Jun12

Table 6-2   Double-blind Treatment Phase Additional Years

Study Visit	Week 4 ± 7 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 16 ± 7 days	Week 20 ± 7 days	Week 24 ± 7 days	Week 28 ± 7 days	Week 32 ± 7 days	Week 36 ± 7 days	Week 40 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	Exit[7]	8 Week Follow Up[9]	Un-scheduled
Protocol Treatments															
Study Agent (Belimumab/Placebo)[5]	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-
AZA administration[6]	X	← Throughout the Study →											-	-	-

Table 6-2 **Footnotes:**

[1] All adverse events (AEs) and serious adverse events (SAEs) that are identified from the start of study agent administration (Day 0) through 8 weeks following administration of the last dose of study agent should be recorded on the Adverse Event Case Report Form (AE eCRF). SAEs that occur after the 8 week follow-up period that are assessed by the investigator as definitely, possibly or probably related to study agent must be reported to the Drug Safety designee on the SAE worksheet. (Post study SAEs will not be documented on the AE eCRF.)

[2] Refer to Appendix 6 for laboratory assessments to be completed.

[3] Results of urine pregnancy test at subsequent visits, if required, must be available prior to dosing. See Section 6.1 (Screening Procedures) for definition of those exempted from pregnancy testing.

[4] Immunogenicity samples are collected pre-dose at all timepoints. For any subject who had a positive antibody response at the 8-week follow-up visit (or last study visit at which immunogenicity was assessed if 8-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or after completion and/or unblinding of the study, whichever is later.

[5] Subjects who discontinue treatment with study agent (belimumab/Placebo) will continue to be followed per this calendar schedule until relapse as defined in Section 8.5.1.

[6] Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1mg/kg/day. If the patient continues to experience the toxicities described above a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted.

[7] Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 1-4 weeks after the last dose of study agent). The Exit Visit should be completed for subjects who discontinue the double blind treatment phase early or when subjects have completed the double-blind treatment phase.   Amend 04 26Feb15

[8] In subjects who discontinue study agent all AEs and SAEs will be reported on the AE eCRF through 8 weeks following administration of the last dose of study agent. After this time, all SAEs, regardless of relationship to study drug, will be collected until relapse or the study is analysed for the primary endpoint, whichever occurs first.   Amend 01 22Jun12

[9] The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent.

[10] Hematology, Modified Chem 20, Urinary protein/urinary creatinine and creatinine clearance are not mandatory at Unscheduled Visits and should be obtained only when determined to be clinically indicated by the Principal Investigator.

[11] Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate.   Amend 02 25Apr13

[12] Complete prior to dosing.

6.4   Unscheduled Visits

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

6.5   Laboratory Tests

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

Due to the potential for unblinding, the following lab results will not be provided to study sites after baseline (Day 0): serum immunoglobulin isotypes IgM/IgA and the results from the FACS analysis listed below.

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

- T cell subsets: CD3+/CD4+, CD3+/CD8+
- B lymphocytes: (CD19+, CD20+, CD20+/CD69+ activated, CD27hi/CD20- short-lived plasma, CD27+/CD20+ memory, CD27-/CD20+ naïve, CD138+/CD20- 138 plasma cells, CD138+/CD20+ plasmacytoid, CD27−/IgD+/CD10+ transitional)

6.5.1 Pharmacokinetics

All randomized subjects who receive a dose of study agent will be sampled for the assessment of serum belimumab levels. A blood sample for pharmacokinetic analysis will be drawn according to the time schedule below.

Table 6-3   PK visit days and sample times

Week	Time (Related to Dosing of Study Agent)
0	Prior to the start of infusion
2	0-4 hours after the end of infusion
8	Prior to the start of infusion
24	0-4 hours after the end of infusion
48	Prior to the start of infusion
24 (of each additional year)	Prior to the start of infusion
48 (of each additional year)	Prior to the start of infusion
Exit visit	Any time during visit
8-week follow-up	Any time during visit

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

6.5.2   Liver Chemistry Stopping and Follow-up Criteria

Amend 02
25Apr13

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

Amend 04
26Feb15

Liver Chemistry Stopping Criteria- Liver Stopping Event	
ALT-absolute	ALT $\geq$ 8xULN
ALT Increase	ALT $\geq$ 5xULN but <8xULN persists for $\geq$2 weeks
	ALT $\geq$ 3xULN but <5xULN persists for $\geq$4 weeks
Bilirubin[1, 2]	ALT $\geq$ 3xULN and bilirubin $\geq$ 2xULN (>35% direct bilirubin)
INR[2]	ALT $\geq$ 3xULN and INR>1.5, if INR measured
Cannot Monitor	ALT $\geq$ 5xULN but <8xULN and cannot be monitored weekly for $\geq$2 weeks
	ALT $\geq$ 3xULN but <5xULN and cannot be monitored weekly for $\geq$4 weeks
Symptomatic[3]	ALT $\geq$ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
1) Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT $\geq$ 3xULN **and** bilirubin $\geq$ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.	
2) All events of ALT $\geq$ 3xULN **and** bilirubin $\geq$ 2xULN (>35% direct bilirubin) or ALT $\geq$ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.	
3) New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).	

6.5.2.1   Required Actions and Follow up Assessments following ANY Liver Stopping Event

ACTIONS:

- Immediately discontinue study treatment

- Report the event to GSK **within 24 hours**

- Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE (All events of ALT $\geq$ 3xULN and bilirubin $\geq$ 2xULN (>35% direct bilirubin) or ALT $\geq$ 3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants)

- Perform liver event follow up assessments

- Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below)

Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 13).

MONITORING

For bilirubin or INR criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours**

- Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline

- A specialist or hepatology consultation is recommended

For All other criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours**

Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline

FOLLOW UP ASSESSMENTS

- Viral hepatitis serology (includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody)

- Blood sample for pharmacokinetic (PK) analysis, obtained within approximately one to two weeks after last dose (PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Fractionate bilirubin, if total bilirubin$\geq$2xULN

- Obtain complete blood count with differential to assess eosinophilia

- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form

- Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications

- Record alcohol use on the liver event alcohol intake case report form

For bilirubin or INR criteria:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).

- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).

Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

6.5.3   Increased Monitoring Criteria with Continued Therapy

If met see required actions below:
- If ALT $\geq$5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks OR

- ALT $\geq$3xULN **and** <5xULN and bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks

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

- Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety.

- Subject can continue study treatment

- Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline

- If at any time subject meets the liver chemistry stopping criteria, proceed as described above for Required Actions and Follow up Assessments following ANY Liver Stopping Event

- If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly.

- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

6.5.4   Study Treatment Restart

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

Approval by GSK for study treatment restart can be considered where:
- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).

- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an HLA genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.

- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.

- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.

- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.

- Study treatment must be administered at the dose specified by GSK.

- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.

- GSK to be notified of any adverse events, as per Section 7.2

6.5.5 Immunogenicity

Serum samples for the measurement of anti-belimumab antibodies will be obtained from all subjects before administration of study agent on Day 0, Week 8, Week 24, Week 48 and Exit/8-week Follow-up. Additionally, samples will be obtained from subjects at Weeks 24 and 48 during additional years. For any subject who had a positive antibody response at the 8-week follow-up visit (or last study visit at which immunogenicity was assessed if 8-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or after completion and/or unblinding of the study, whichever is later.

6.6   Exit Visit

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

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an attempt will be made to ascertain survival status at 12 months after the first dose of study agent.

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

6.7   8-Week Follow-up Visit

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

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

6.8   Withdrawal of Subjects from Treatment

Subjects will be free to withdraw from treatment or from the study at any time, for any reason, or they may be withdrawn/removed, if necessary, to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

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

- Unacceptable toxicity (see Section 5.4)
- Prohibited concurrent medication or therapy (see Section 5.5.1 and Section 5.5.2)
- Withdrawal of consent (including use and disclosure of research-related health information)
- Pregnancy

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an attempt will be made to ascertain survival status 12 months after the first dose of study agent. Any subject that withdraws consent for use and disclosure of research-related health information will be considered withdrawn from the study and not followed.

6.9   Subject Unblinding

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

If a medical emergency occurs and a decision regarding the subject's condition requires knowledge of the treatment assignment, the study blind may be broken for the specific subject. Whenever possible, the investigator should consult with the medical monitor prior to unblinding any subject. Any broken blind will be clearly justified and explained by a comment in the eCRF. The investigator must notify the Medical Monitor of any broken blind, regardless of whether it was done for emergency or non-emergency reasons.

7 Adverse Event Reporting

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

7.1   Definitions

ADVERSE EVENT

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

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

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study

- Signs, symptoms, or the clinical sequelae of a suspected interaction

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

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

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

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

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

a. Results in death

b. Is life-threatening

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

c. Requires hospitalization or prolongation of an existing hospitalization

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

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

d. Results in disability / incapacity, or

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

e. Is a congenital anomaly / birth defect

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

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

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

7.2   Reporting Adverse Events to the Sponsor

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

For subjects who discontinue treatment with study agent during the double-blind period (for reasons other than withdrawal of consent), all adverse events will be collected through 8 weeks following the administration of the last dose of study agent. After this time, all SAEs, regardless of relationship to study drug, will be collected until relapse or the study is analysed for the primary endpoint and study sites are informed that SAE data collection can cease, whichever occurs first.

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

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

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

7.3   Other Events Requiring Rapid Reporting (Protocol Specified Events)

Protocol Specified Events (PSEs) are additional events that must be reported to the Drug Safety designee in an expedited manner. A PSE may or may not be an SAE. PSEs are considered SAEs if they meet 1 or more of the criteria for an SAE (See Section 7.1). PSEs are

recorded on the PSE page of the eCRF within 24 hours of site personnel becoming aware of the event.

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

7.4   Laboratory Abnormalities as Adverse Events

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

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

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

7.5   Progressive Multifocal Leukoencephalopathy

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Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. A diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The subject should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping all immunosuppressant therapy.

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If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

7.6   Suicidality Assessment

Some autoimmune diseases have an increased risk of suicidal behavior and/or ideation (Bachen et al, 2009, Timonen et al, 2003, Stenager et al, 1992). In order to objectively assess suicidality in belimumab clinical programs the C-SSRS will be utilized to collect information on suicidal behavior and ideation. Since major depressive disorder may increase the risk of suicidal ideation or behavior before or during clinical studies, subjects participating in this study will be assessed at every visit for suicidality.

Subjects who answer "yes" to any suicidal behavior or "yes" to suicidal ideation questions 4 or 5 on the C-SSRS should be referred to appropriate psychiatric care and prompts the completion of an SAE worksheet. The medical monitor should be notified when these events occur. In addition, a "yes" to any suicidal behavior or "yes" to suicidal ideation question 3, 4 or 5 on the C-SSRS prompts the completion of the Possible Suicidality Related History Questionnaire (PSRHQ, only the first time this condition is met; refer to Appendix 10 for the PSRHQ) eCRF and a Possible Suicidality Related Questionnaire (PSRQ) eCRF (at all times this condition is met; refer to Appendix 11 for the PSRQ).

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

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Although assessment of suicidality using the C-SSRS will take place only during the blinded portion of the study, investigators are reminded of the importance to clinically assess for suicidality at every visit given that study patients are at increased risk of suicidal behavior and/or ideation.

7.6.1 Possible Suicidality Related Questionnaire (PSRQ)

The investigator will be prompted to complete the PSRQ (in addition to the AE or SAE pages, as appropriate) if a yes response is given to any suicidal behavior or a yes response to suicidal ideation questions 3, 4 or 5 on the C-SSRS. Refer to Appendix 11 for the PSRQ. If the adverse event meets the definition of an SAE, which includes a yes answer to any suicidal behavior or a yes to suicidal ideation questions 4 or 5 on the C-SSRS the site must ensure that there are no significant discrepancies between the PSRQ and the SAE.

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7.7   Reporting a Pregnancy

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Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to the Sponsor within 2 weeks of learning of its occurrence. All pregnancies that are identified from the start of study agent through 16 weeks following the last dose of study agent should be reported. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

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

7.8   Investigator Evaluation of Adverse Events

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

SEVERITY

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

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

CAUSALITY

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.9   Follow-Up of Adverse Events

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Serious and non-serious adverse events that occur from the start of study medication administration through 8 weeks after the date of last administration of study agent are reported.

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

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

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

All SAEs that are considered by the sponsor to be unexpected and related to belimumab will be reported by the sponsor or designee as expedited (eg, 15-Day) reports to the appropriate regulatory authorities AND to all participating investigators (exceptions discussed below). In addition, the sponsor or designee follows all applicable local and national regulatory requirements regarding safety reporting. Each investigator must also comply with the applicable regulatory requirements related to the reporting of SAEs to the IRBs/IECs responsible for reviewing the study at their site, as well as the regulatory authority(ies) (if applicable).

All serious adverse events, including serious disease-related events (discussed below), will be monitored by treatment group by an independent DMC. Investigators and IRBs/IECs will be notified of the outcome of each DMC meeting, and any recommendations made.

The conditions listed in Appendix 3 are disease related events that can occur in the study population regardless of belimumab exposure. When these conditions are considered SAEs, they must be reported to the Sponsor within 24 hours of site personnel becoming aware as described in Section 7.2. Where these are clearly related to the underlying vasculitis, the Sponsor may not submit them as expedited reports to regulatory authorities or participating investigators.

8 Endpoints and Statistical Analysis

8.1 General Statistical Considerations

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

The database will be locked for the primary analysis after all data have been collected, verified and validated for all subjects through 12 months after the randomization of the last subject. All subjects and study site personnel will remain blinded to original treatment assignment until after the final database is locked and the results of the study are made publicly available.

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Analysis of primary and secondary endpoints will be exploratory in nature. Nominal p values may be reported and considered descriptive. Where appropriate point estimates and 95% confidence intervals will be constructed.

8.2 Randomization Procedure and Assignment to Treatment Groups

This is a multi-center, multinational, randomized, double-blind, placebo-controlled study. Once subjects have consented, have undergone all screening procedures and have been determined to be eligible for the study, they will be randomly assigned (via an interactive web response system [IWRS]) to 1 of 2 treatment groups (belimumab [10 mg/kg] or placebo) in a 1:1 ratio. At randomization, subjects will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. RTX). Randomization will be performed on Day 0.

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8.3 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will review safety data on an ongoing basis until the data are locked and analyzed (after which monitoring may be assumed by an internal HGS committee). The DMC will include at least 3 physicians and a statistician, none of whom are affiliated with the Sponsor. Initial randomization will be limited to 40 subjects per induction regimen (40 post-RTX induction and 40 post-CYC induction). The first DMC reviews will occur after the first 20 subjects per induction regimen (RTX or IV/oral CYC) have been randomized and have had a Week 8 visit. Once the first 20 subjects randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the DMC, who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with CYC. The DMC will review the data approximately every 6 months thereafter across both induction regimens. At all times the sites and sponsor will remain blinded to treatment allocation. Investigators and IRBs/IECs will be notified of the outcome of each DMC meeting.

The DMC will receive information within 72 hours of the sponsor or designee receiving notification of any IgG < 250 mg/dL and all unexpected causally-related SAEs that are life threatening or result in death. Other unexpected, causally-related SAEs will be provided to the DMC within 15 calendar days. In addition, the DMC will receive information on all serious infections and all opportunistic infections, irrespective of relationship to study agent, within 15 calendar days.

8.4   Sample Size Rationale

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Approximately 100 subjects will be randomized. The sample size has been determined based on the feasibility of enrolling patients into the study within a reasonable time-frame. The sample size was not based on statistical considerations and the analysis of primary and secondary endpoints will be exploratory in nature. The primary efficacy analysis will be performed after 12 months have elapsed following randomization of the last subject.

Although the sample size is based on feasibility, the minimal detectable effect has been determined. Assuming an observed relapse rate at 18 months of 20% in the placebo group, a relapse rate of $\leq 7.0\%$ on belimumab (hazard ratio ≤ 0.32) would be statistically significant ($p < 0.05$) in a study of 100 subjects (50 per arm).

8.5   Efficacy

8.5.1 Primary Efficacy Endpoint

The primary endpoint is time from Day 0 to the first relapse, defined as

- at least 1 major BVAS item (Appendix 4) OR
- a minimum total BVAS score of 6 (Appendix 4) OR
- receipt of prohibited medications (as defined in Section 5.5.1).

8.5.2 Primary Efficacy Analysis

The primary efficacy analysis will compare the time to first relapse from Day 0 between the placebo/azathioprine group and the belimumab/azathioprine combination group using a Cox proportional hazard model, adjusted for ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide). However, the adjustment of induction regimen will be changed to rituximab vs. IV and/or oral cyclophosphamide if the number of events (relapse) is less than 5 in subjects using the oral or IV cyclophosphamide. If there are then still less than 5 patients with an event (relapse) in any of the levels of this or any other stratification factor then the stratification term may be removed from the model. For any subject who does not experience a relapse, the time to first relapse will be censored at the time of the subject's last assessment. Subjects who discontinue study agent prior to relapse/flare (as defined in primary efficacy endpoint) are to be followed per protocol for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The database will be locked and the primary efficacy analysis will be performed after 12 months have elapsed following randomization of the last subject.

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8.5.3 Major Secondary Efficacy Endpoint

1. Time from Day 0 to the first major relapse (defined as experiencing at least 1 major BVAS item).

8.5.4 Other Efficacy Endpoints

1. Time from Day 0 to first minor or major relapse (defined as experiencing at least 1 minor BVAS item and/or using a dose of rescue medication).
2. Absolute change in Vasculitis Damage Index (VDI) at double-blind Week 48 of Year 1 and double-blind Week 28 of Year 2 and by visit;
3. Proportion of subjects with any increase in VDI at double-blind Week 48 of Year 1 and double-blind Week 28 of Year 2 and by visit;
4. Absolute change in BVAS at double-blind Week 48 of Year 1 and double-blind Week 28 of Year 2 and by visit;
5. Proportion of subjects with any increase in BVAS at double-blind Week 48 of Year 1 and double-blind Week 28 of Year 2 and by visit; and
6. Proportion of subjects with any increase in BVAS organ domains at double-blind Week 48 of Year 1 and double-blind Week 28 of Year 2 and by visit and by domain.
7. Proportion of patients in remission (defined as BVAS=0 and corticosteroid dose < 10 mg/day) at double-blind Week 48 of Year 1, double-blind Week 28 of Year 2 and by visit.
8. Proportion of patients with no relapse at double-blind Week 48 of Year 1, double-blind Week 28 of Year 2 and by visit.

Biological Markers and Autoantibodies:

Pharmacogenetic sampling (in consenting subjects) will be taken once during the course of this study (see Appendix 9).

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

- Anti-neutrophil cytoplasmic antibody (ANCA – anti-PR3, anti-MPO)
- Serum complement (C3, C4)
- Serum immunoglobulin isotypes (IgA, IgM, IgG)
- C-reactive Protein (CRP)
- Erythrocyte sedimentation rate (ESR)
- Urinary protein: urinary creatinine ratio
- BLyS protein (Day 0 only)

- FACS of peripheral lymphocytes:
  B lymphocytes (CD19+, CD20+, CD20+/CD69+ activated, CD27hi/CD20- short-lived plasma, CD27+/CD20+ memory, CD27-/CD20+ naïve, CD138+/CD20- 138 plasma cells, CD138+/CD20+ plasmacytoid, CD27−/IgD+/CD10+ transitional)
  T cell subsets: CD3+/CD4+, CD3+/CD8+

8.5.5 Major Secondary Endpoint analysis and Other Efficacy Analyses

The exploratory analysis of the major secondary efficacy endpoint will be performed using the same method described for the primary efficacy endpoint, but censoring subjects who receive any prohibited medication (as defined in Section 5.5.1) prior to an observation of any major BVAS item. Any censoring will be applied on the date prohibited medications are received.

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The analysis of other efficacy endpoints, biomarkers, and auto-antibodies measurements will be described in the statistical analysis plan.

8.6   Safety

8.6.1 Definition of Safety Variables

Safety will be evaluated by adverse events, changes in laboratory parameters, suicidality assessment (Appendix 8), and immunogenicity.

8.6.2 Analysis of Safety Variables

AEs will be graded for severity by the investigator using Adverse Event Severity Grading Tables (Appendix 7) or as described in Section 7.8, as appropriate. The frequency and rate of AEs will be tabulated by MedDRA system organ class (SOC) and preferred term. Additional analyses may be performed based on event rates adjusting for subject-years on study agent if the time on study agent is imbalanced across treatment groups. Serious and severe (Grade 3 and Grade 4) AEs will also be summarized by MedDRA SOC and preferred term. Discontinuations due to AEs will be summarized.

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

Safety Endpoints of Special Interest

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

- Infusion reactions including hypersensitivity reactions
- Immunogenicity

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

8.7 Pharmacokinetics

8.7.1 Definition of Pharmacokinetic Evaluation

All randomized subjects who receive a dose of study agent will be sampled for the assessment of serum belimumab levels. Assessment of belimumab concentrations will be performed at the timepoints indicated in Section 6.5.1.

8.7.2 Analysis of Pharmacokinetics

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

9 Pharmacogenetics (PGx)

In consenting subjects, a blood sample for PGx research will be drawn at baseline (Day 0) to better characterize genetic variability (eg, HLA typing) that may affect efficacy or safety endpoints. Information regarding PGx research is included in Appendix 9.

The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the study site. The approval(s) must be in writing and clearly specify approval of the PGx assessments (ie, approval of Appendix 9). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate that approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments are not approved, then approval for the rest of the study will clearly indicate this and that PGx assessments will not be conducted.

10 Study Administration

Belimumab is under joint development by Human Genome Sciences, Inc and GlaxoSmithKline Pharmaceuticals. Human Genome Sciences, Inc. is the sponsor of the study.

10.1 Informed Consent

A copy of the proposed informed consent document must be submitted to the Sponsor or designee for review and comment prior to submission to the reviewing IRB/IEC. The consent

form must be approved by the IRB/IEC and contain all elements required by national, state, local, and institutional regulations or requirements.

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

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

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

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

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

10.3 Protocol Compliance

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

10.4 Protocol Revisions

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

10.5 Data Collection and Management

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

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

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

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

10.6 Study Monitoring

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

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

10.7   Drug Accountability

Upon receipt, the investigator is responsible for taking an inventory of the study agent, including any buffers or diluents. A record of this inventory must be kept and usage must be documented on study agent inventory forms provided by the Sponsor.

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

10.8   Retention of Records

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

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

10.9   Financial Disclosure

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

10.10 Publication Policy

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

The investigator shall submit a copy of any proposed publication, manuscript, abstract, presentation or other document with respect to this study to the Sponsor for review and comment at least 60 days prior to its submission for publication or presentation. No publication or presentation with respect to the study shall be made unless and until all of the

Sponsor's comments on the proposed publication or presentation have been considered and any information determined by Sponsor to be confidential information has been removed. If requested in writing by the Sponsor, the investigator shall withhold material from submission for publication or presentation for an additional 60 days to allow for the filing of a patent application or the taking of other measures to establish and preserve the Sponsor's proprietary rights.

10.11 Study or Study Site Termination

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

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of HGS to suspend or discontinue testing, evaluation, or development of the product for WG or MPA.

The study site may warrant termination under the following conditions:

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

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Amend 02
25Apr13

Amend 03
04Feb14

Amend 04
26Feb15

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List of Appendices

**Appendix 1   Chapel Hill Consensus Definition for Granulomatosis
with polyangiitis (GPA) (Wegener's Granulomatosis)
(Jennette et al, 2013)**

The CHCC Definition requires:

Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium-sized vessels (eg, capillaries, venules, arterioles, and arteries) for a diagnosis of Wegener's.

Another feature that may be commonly present in GPA, but which is not required according to the CHCC definition, is necrotizing glomerulonephritis.

Appendix 2   Chapel Hill Consensus Definition for Microscopic Polyangiitis (MPA) (Jennette et al, 2013)

The CHCC definition requires:

Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (ie, capillaries, venules, or arterioles) for a diagnosis of MPA. Granulomatous inflammation is absent.

Other features that may be present in MPA, but that are not required according to the CHCC definition, are: necrotizing arteritis involving small- and medium-sized arteries; commonly necrotizing glomerulonephritis; and often pulmonary capillaritis.

Appendix 3   BVAS Activity Assessment Form

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

Appendix 4   BVAS Item Scoring

Appendix 5   Vasculitis Damage Index

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

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04Feb14

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| Protocol Identifier | BEL115466 |

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VASCULITIS DAMAGE INDEX (VDI)
INVESTIGATOR INSTRUCTIONS

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

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Protocol Identifier	Subject Identifier	Date of Assessment			Visit Description ✓ one:		
		Day	Month	Year			
BEL115466					☐ Screening ☐ Day 0	☐ Year____ ☐ Week 12 ☐ Week 24 ☐ Week 36 ☐ Week 48 ☐ Exit	☐ OL Day 0 ☐ OL Week 24 ☐ OL Week 28/Exit

VASCULITIS DAMAGE INDEX (VDI)

Appendix 6   Laboratory Tests[1]

Hematology
Total white blood cell count
Differential:
  Absolute Neutrophils
    Segmented Neutrophils
    Band Neutrophils
    Myelocytes
    Metamylocytes
    Promyelocytes
  Lymphocytes
  Monocytes
  Eosinophils
  Basophils
Hemoglobin
Hematocrit
Red blood cell (RBC) count
Platelet count
Prothrombin time (PT)
Partial thromboplastin time (PTT)
INR
Serum Pregnancy

Biological Markers

FACS of peripheral lymphocytes:
T cell subsets: CD3+/CD4+, CD3+/CD8+
B lymphocytes (CD19+, CD20+, CD20+/CD69+ activated, CD27hi/CD20- short-lived plasma, CD27+/CD20+ memory, CD27-/CD20+ naïve, CD138+/CD20- 138 plasma cells, CD138+/CD20+ plasmacytoid, CD27−/IgD+/CD10+ transitional)

BLyS protein
Serum complement (C3 and C4)
C-Reactive Protein (CRP)
Erythrocyte sedimentation rate (ESR)

Immunoglobulins
Serum immunoglobulin isotypes: IgG, IgM, IgA

PK and Immunogenicity

Autoantibodies
ANCA (anti-PR3; anti-MPO)

Urinalysis
Protein
Glucose
Ketones
Occult blood
Microscopic examination including:
  WBC per hpf
  RBC per hpf
  Casts (specified by type eg, RBC, WBC)
Spot Urine (protein : creatinine ratio)
Urine Pregnancy

Modified Chem-20
Electrolytes:
  Sodium
  Potassium
  Magnesium
  Chloride
  Carbon dioxide
  Calcium adjusted for Albumin
  Inorganic Phosphate   Amend 01 22Jun12
Enzymes:
  SGOT (AST)
  SGPT (ALT)
  Alkaline Phosphatase
  Gamma glutamyl transferase (GGT)
  Lactate dehydrogenase (LDH)
Other:
  Creatinine
  Blood urea nitrogen (BUN)
  BUN/creatinine ratio
  Bilirubin, total
  Protein, total
  Albumin
  Uric acid
  Glucose
  HIV-1/2 antibody   Amend 02 25Apr13
  Hepatitis C antibody (± HCV RNA PCR for confirmation of positive antibody test)
  Hepatitis B surface antigen
  Hepatitis B surface and core antigen antibodies   Amend 02 25Apr13
  Estimated Creatinine Clearance/ GFR (Cockcroft-Gault)

Liver event follow-up assessments: Amend 02 25Apr13
  Hepatitis A IgM antibody
  HBsAg and HB Core antibody (IgM)
  Hepatitis C RNA
  Cytomegalovirus IgM antibody
  Epstein-Barr viral capsid antigen IgM antibody
  Hepatitis E IgM antibody
  CPK
  Anti-smooth muscle antibody
  Type 1 anti-liver kidney microsomal antibodies   Amend 02 25Apr13

[1]Institution or country specific guidelines for blood sample volume limits must be followed in collection of the subsequent blood sample.

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Appendix 7   Adverse Event Severity Grading Tables

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

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

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

Modified from DMID Adult Toxicity Tables, 2001

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

(continued)

Modified from DMID Adult Toxicity Tables, 2001

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

*(Goldfarb et al, 2001; Yamani et al, 2001; Eibl and Rosen, 1995).   Modified from DMID Adult Toxicity Tables, 2001

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

Modified from DMID Adult Toxicity Tables, 2001

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

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

RBC = red blood cell; hpf = high power field.   Modified from DMID Adult Toxicity Tables, 2001

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

Modified from DMID Adult Toxicity Tables, 2001

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

Modified from DMID Adult Toxicity Tables, 2001

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

Appendix 9   Pharmacogenetic Research

Background

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

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

Research Rationale

Systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies but little is known regarding the genetic contribution to risk for developing different forms of vasculitis. Recent gene studies in vasculitis are identifying both common polymorphisms associated with other autoimmune but also completely different associations (Monach and Merkel, 2010).

Amend 02
25Apr13

There is growing evidence for a genetic contribution to the risk of developing different forms of vasculitis (Monach and Merkel, 2010) for example the association of alpha 1-antitrypsin deficiency in WG.

Amend 02
25Apr13

Blood samples for pharmacogenetics will be drawn as described in Section 9. Insights into the genetic pathways underlying AAV may help identify subgroups of patients that may have additional benefit from therapies from specific therapies. Fc Receptor polymorphism analysis may further define the interaction between underlying genetic heterogeneity and the therapeutic endpoints utilized in this trial.

Collection of whole blood samples may enable PGx analyses to be conducted if there are any unexplained or unexpected results.

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

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

Study Population

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

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

Informed Consent

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

Study Assessments and Procedures

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

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

The need to conduct PGx analysis may be identified after a study (or set of studies) of belimumab has been completed and the study data reviewed. In some cases, the samples may not be studied ie, no questions are raised about how people respond to belimumab.

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

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

Subject Withdrawal from Study

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

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

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

Screen and Baseline Failures

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

Pharmacogenetics Analyses

Specific sections of DNA may be selected from areas of the genome (ie, candidate genes) known to encode the drug target, drug metabolizing enzymes, areas associated with mechanisms underlying adverse events, and those linked to study disease and, thus, linked to drug response.

Generally, two approaches will be utilized to explore genetic variation in drug response.

The candidate genes that may be selected and investigated in this study are the following:

- HLA alleles
- Alpha-1 anti-trypsin (A1AT)
- Fc receptors
- Cytokines, immune receptors and chemokines related to immune cell function

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

By evaluating large numbers of polymorphic markers (eg, single nucleotide polymorphisms or SNPs) throughout the genome, sets of markers may be identified that correspond to differential drug response. These will include:

- **Hardy-Weinberg Equilibrium Testing**

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

- **Comparison of Demographic and Baseline Characteristics by Genotype**

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

- **Evaluation of Genotypic Effects**

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

- **Evaluation of Treatment by Genotype and Gene-Gene Interaction**

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

- **Linkage Disequilibrium**

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

- **Multiple Comparisons and Multiplicity**

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

- **Power and Sample Size Considerations**

  The ability to detect differential drug response among genotypes at a polymorphic site depends on the total number of subjects genotyped and the frequency distribution of the different genotypes. Consequently, genotyping analyses are plausible for those polymorphic sites where the number of subjects comprising the genotypic groups is sufficiently large; however, these frequencies will not be known until sufficient samples have been collected and genotyping is complete.

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

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

Appendix 10   Possible Suicidality Related History Questionnaire (PSRHQ)   Amend 02
25Apr13

gsk GlaxoSmithKline	CONFIDENTIAL		Final - 16 JAN 13
	Protocol Identifier	**BEL115466**	

POSSIBLE SUICIDALITY-RELATED HISTORY QUESTIONNAIRE (PSRHQ) INSTRUCTIONS

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

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

And/or

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

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

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

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

gsk GlaxoSmithKline   CONFIDENTIAL   Final - 16 JAN 13

Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
BEL115466			

Date of assessment [ ] [ ] [ ] Day Month Year

POSSIBLE SUICIDALITY-RELATED HISTORY QUESTIONNAIRE

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

[Y] ☐ Yes   [N] ☐ No

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

	Event	Date (DDMMMYYYY)
☐	Cerebrovascular Accident	
☐	Headache	
☐	Meningitis	
☐	Organic Confusion	
☐	Seizures	

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

Appendix 11   Possible Suicidality Related Questionnaire (PSRQ)

	CONFIDENTIAL	
Protocol Identifier	**BEL115466**	

gsk GlaxoSmithKline   Final - 15 JAN 13

POSSIBLE SUICIDALITY-RELATED QUESTIONNAIRE (PSRQ)
INSTRUCTIONS

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

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

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

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

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

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

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

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

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

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

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Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
BEL115466			

Date of assessment [ ] [ ] [ ] Day Month Year

POSSIBLE SUICIDALITY-RELATED QUESTIONNAIRE (PSRQ)

☐ Not Done

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

If Yes, check all that apply:

☐ Amphetamines ☐ Benzodiazepines ☐ Cannabinoids ☐ Cocaine ☐ Opiates

☐ Other, Specify: _____

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

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

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

If Yes, check all that apply:

☐ Family Problems ☐ Relationships ☐ Employment/ Unemployment ☐ Finances

☐ Other Factors, Specify:_____

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

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

Father ☐ Ideation ☐ Behavior

Mother ☐ Ideation ☐ Behavior

Sibling ☐ Ideation ☐ Behavior

Other ☐ Ideation ☐ Behavior

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

If Yes, specify disorder next to all that apply:

Father _____

Mother _____

Sibling _____

Other _____

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

Appendix 12   Protocol Addendum – Benefit and Risk Assessment

Disease Background

The systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies including infective and drug-induced causes and can be either primary or secondary to other diseases such as SLE. A subset of the primary small vessel vasculitides: Wegener's granulomatosis; also known as granulomatosis with polyangiitis (GPA), microscopic polyangiitis and Churg-Strauss syndrome (CSS), are characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) (Jennette and Falk, 1997). ANCA-associated vasculitides (AAV) are multisystem diseases with a broad range of manifestations from cutaneous ulcers, scleritis, pericarditis to lifethreatening manifestations such as lung hemorrhage and renal failure. All 3 forms of AAV share the characteristic of systemic necrotizing vasculitis; WG and CSS are further characterized by granuloma formation.

Historically, ANCA have been classified on the basis of their staining patterns in immunofluoresence assays as either cytoplasmic (C-ANCA) or perinuclear (P-ANCA). It is now recognized that in AAV, C-ANCA is usually directed against proteinase 3 (PR3), and P-ANCA is generally directed against myeloperoxidase (MPO), both of which are enzymes that are abundant in the granules of neutrophils (Jennette and Falk, 1997; Merkel et al, 1997). Anti-PR3 antibodies are generally associated with WG, while anti-MPO autoantibodies are more common in MPA and CSS. Anti-PR3 antibodies are associated with increased morbidity and mortality compared to anti-MPO. The most widely used classification criteria for diagnosing the 3 types of AAV are those published by the American College of Rheumatology (ACR) for WG and CSS (Leavitt et al, 1990 and Masi et al, 1990, respectively), and that published by the Chapel Hill Consensus Conference (CHCC) for MPA (Jennette et al, 1994). Of note, none of these diagnostic criteria incorporate the measurement of ANCA.

The precise epidemiology of these diseases is uncertain as early studies did not utilize the same classification criteria as later ones (Koldingsnes and Nossent, 2008; Watts et al, 2007). In the case of MPA, in particular, epidemiological studies are confounded by its original inclusion as a form of polyarteritis nodosa (PAN). Utilizing the ACR or CHCC criteria, prevalence rates range from 5-16/100000 for WG, 2.5-9.4/100000 for MPA, and 0.4-1.4/100000 for CSS making the latter the least prevalent of the three by some margin (Koldingsnes et al, 2008). AAV are extremely rare in childhood with peak age of onset in those aged 65 to 74 years (Ntatsaki et al, 2010), with other small vessel vasculitides being the major concern in childhood (Brogan et al, 2010).Current therapy is usually determined by severity of the disease, with more severe forms warranting more aggressive approaches. These usually involve an initial remission induction regimen of high dose corticosteroid administered with either cyclophosphamide (CYC) or rituximab (RTX) followed by a remission maintenance period usually with azathioprine (Stone et al, 2010; Bosch et al, 2007; Jayne et al, 2003). Minor manifestations are usually treated with low dose corticosteroid administered with either azathioprine or methotrexate (Belmont, 2006). Even with recent

treatment advances the morbidity and mortality of patients with AAV remains unacceptably high (Drooger et al, 2009).

The Birmingham Vasculitis Activity Score (BVAS) was developed and validated as a tool to measure disease activity (Luqmani et al, 1994). It has been modified to form the BVAS/WG (Stone et al, 2001) and updated most recently with the validation of version 3 of the instrument, also known as BVAS 2003 (Mukhtyar et al, 2009). In its current form it is a list of 56 items which are considered to be manifestations of vasculitis. A weighted numerical score is attached to each item to reflect the importance of each manifestation. The items are grouped by organ systems, and each organ system has a maximum or 'ceiling' score to reflect the relative importance of the organ system (Mukhtyar et al, 2009). The tool also makes a distinction between new or worsening disease and persistent disease with new or worsening attracting higher scores.

IV Belimumab

Over 2,000 individuals with SLE have been treated with belimumab in clinical studies. In two global Phase 3 studies, belimumab 10 mg/kg met the primary efficacy endpoint (SRI at Week 52). Evidence of other possible benefits in these trials included reductions in risk of severe flare and corticosteroid use, and improvements in patient reported quality of life and fatigue. Serological activity was reduced as measured by reductions in autoantibodies and normalization of hypergammaglobulinemia and complement levels. B cells, including autoreactive B cells, were also reduced, but not severely depleted, consistent with what would be expected from inhibition of BLyS (reference belimumab IB, Section 5.3.1). These results supported the approval of belimumab in the EU, US, Canada and other countries.

In the United States belimumab is approved for the following indication:

> *BENLYSTA® (belimumab) is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.*

> *Limitations of Use: The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of BENLYSTA is not recommended in these situations.*

In the EU, the approved indication focuses on patients with high disease activity (where belimumab offered the greatest benefit):

> *Benlysta is indicated as add-on therapy in adult patients with active, autoantibodypositive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g positive anti-dsDNA and low complement) despite standard therapy.*

The EU SPC also includes special warnings and precautions for use similar to the US labeling, including that belimumab has not been studied in and is thus not recommended in

patients with severe active central nervous system lupus or severe active lupus nephritis. In addition, caution should be exercised if belimumab is co-administered with other B cell targeted therapy or cyclophosphamide. Reference Section 4.4 of the SPC for the complete list of specials warnings and precautions.

Treatment with belimumab plus standard therapy was generally well tolerated, with rates of AEs, severe AEs, SAEs, AEs leading to discontinuation, and serious/severe infections generally comparable to the rates observed in the placebo plus standard therapy group. The most commonly-reported adverse reactions, occurring in $\geq$ 3% of patients receiving 10 mg/kg belimumab IV in clinical trials (and at a $\geq$ 1% greater rate than placebo) were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, cystitis, leukopenia, and gastroenteritis viral. In clinical trials, hypersensitivity and infusion reactions were observed more frequently with belimumab, with anaphylaxis observed in $\leq$ 1% of subjects. Data from the post-marketing setting indicate that hypersensitivity reactions may be serious or result in death, that the onset of such reactions may be delayed, and that patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. In addition, it is also known from clinical trials and the post-marketing setting that the vast majority of hypersensitivity reactions occur with the 1st or 2nd infusion. The product labeling, belimumab IB, protocol, and informed consent forms have been updated to include this new information, as applicable.

Other risks that may be associated with belimumab based on its mechanism of action include serious infections and malignancy, although no increases in the rates of serious infections or malignancies have been observed. Psychiatric events including depression and suicide were observed more frequently with belimumab than with placebo, although it is unknown if belimumab treatment is associated with an increased risk for these events. Finally, mortality rates in the controlled clinical trials were low, although numerically higher in the belimumab groups (0.4% and 0.8% in the placebo and belimumab groups, respectively). Causes of death were as expected in an SLE population with active disease receiving a wide range of standard therapies, such as corticosteroids and immunosuppressants, and included infection, cardiovascular disease, and suicide.

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in patients with SLE receiving immunosuppressant pharmacotherapy, including belimumab. Although the benefit-risk profile for belimumab remains unchanged following these events, the Sponsor considers that knowledge of these cases is important and has updated the clinical investigator's brochure (IB) for belimumab and revised the informed consent form (ICF) to communicate that development of PML is a potential risk. Amend 03 04Feb14

Experience from open-label, long-term continuation trials of belimumab in SLE patients suggests prolonged treatment with belimumab remains generally well tolerated, with no apparent increase in the incidence of AEs or 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.

Belimumab in ANCA-Associated Vasculitis

Study Overview and Patient Population

Belimumab at a dose of 10 mg/kg in combination with standard SLE therapy demonstrated a statistically significant and clinically meaningful reduction in SLE disease activity versus placebo plus standard SLE therapy at Week 52 in two Phase 3 clinical studies in subjects with active, autoantibody-positive SLE.

Studies in subjects with WG and MPA have shown the need for more effective treatment for the maintenance of remission, with relapse rates with these 2 diseases ranging from 15% at 18 months (Jayne et al, 2003) to 38% at 3 years (Hiemstra et al, 2010) on azathioprine – the most effective of current therapies (Jayne et al, 2003; Pagnoux et al, 2008; Hiemstra et al, 2010).

The presence of ANCA autoantibodies in AAV implicates B cells in the pathogenesis of AAV. Further supporting a role for B cells is the fact that activated B cells are present in greater numbers in GPA subjects compared with healthy persons (Popa et al, 1999). Additionally, elevated levels of BLyS, a B cell survival factor, are found in subjects with AAV (Krumbholz et al, 2005; Nagai et al, 2011; Schneeweis et al, 2010). Together, these provide a strong pharmacologic rationale for the use of belimumab to treat AAV, since belimumab has been shown in SLE to reduce both B cells and autoantibody levels. Therefore, for the proposed study, subjects are required to have documented evidence of anti-PR3 or anti-MPO autoantibodies prior to randomization, as this population is considered the most likely to benefit from treatment with a B cell modulating agent like belimumab. This is consistent with the Phase 3 SLE results for belimumab where the subjects who benefitted from treatment were those who were antinuclear antibody (ANA/anti-dsDNA) autoantibody positive at baseline.

The fact that rituximab, a biologic therapy that targets B cells by binding to the B cell surface antigen CD20, recently showed success in inducing remission in AAV (Stone et al, 2010) and was granted approval in the US for the treatment of WG and MPA supports the rationale that belimumab, which down regulates B cells by targeting BLyS, may be useful in the treatment of this disease. Finally, limited data from the small (n = 111) subset of subjects in the Phase 3 trials of SLE who had vasculitic symptoms as part of their SLE (as assessed by the SELENA SLEDAI) showed that more subjects in the belimumab plus standard of care treatment arms had resolution of their vasculitic symptoms at Week 52 compared with subjects receiving placebo plus standard of care. Specifically, 19/36 (52.8%) and 28/38 (73.7%) of subjects in the belimumab 1 mg/kg and 10 mg/kg dose groups, respectively, had resolution of vasculitic activity at Week 52 compared with 15/37 (40.5%) of placebo subjects. Taken together, these data support the evaluation of belimumab in AAV.

The safety of the proposed study is supported by data from the Phase 2 and 3 trials in SLE in which subjects who were receiving belimumab in combination with significant background therapies, including steroids and immunosuppressants, had an adverse event profile similar to that of subjects receiving placebo plus standard therapies.

This is a multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen. Subjects enrolled into the study must have a clinical diagnosis of WG or MPA according to the Chapel Hill criteria and must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either CYC or RTX in the 6 months leading up to randomization. Subjects treated with 1 of the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR
- CYC 2 mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

[*The cyclophosphamide dosing regimens are provided as targets but may be adjusted for older age, obesity, renal insufficiency, leukopenia, or other toxicities as dictated by local practice.*]

For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 0.5-1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ≤ 10 mg/day. As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.

Approximately 100 subjects with ANCA-vasculitis who are between 6 and 26 weeks from starting induction therapy, who achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving ≤10 mg/day prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart will be enrolled into the study. Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter. Randomization will be performed on Day 0.

All subjects (in both the belimumab and placebo groups) will be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. For the maintenance of remission, azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine must not be initiated any later than Day 0. For subjects previously identified as

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being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset. Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above, a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis.

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV CYC vs. oral CYC vs. RTX). It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Refer to Section 4 of Protocol HGS1006-C1100 for a complete list of inclusion and exclusion criteria.

The primary efficacy endpoint is time from Day 0 to the first relapse, defined as at least 1 major BVAS item or a minimum total BVAS score of 6 or receipt of prohibited medications according to the protocol. Subjects will receive study agent (belimumab/placebo) plus AZA until the results from the primary efficacy analysis are available or until they experience a flare (relapse) as defined in the primary efficacy endpoint. The database will be locked and the primary analysis will be performed when 12 months have elapsed after the last subject is randomized. Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an attempt will be made to ascertain survival status at 12 months after the first dose of study agent.

All subjects will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent.

Dose and Schedule

Investigational Study Agent (Belimumab or Placebo)

The dose and schedule of belimumab proposed for use in the ANCA-associated vasculitis study is the same dosage (10 mg/kg every 2 weeks for 3 doses and every 4 weeks thereafter) and route of administration (IV) as that approved for marketing. The belimumab BDS and FDP that will be used for this study is the same as that approved for marketing.

In the Phase 3 IV SLE studies, several clinical measures of improvement including the primary efficacy endpoint at Week 52 (SRI), SELENA SLEDAI reductions, severe flare risk reduction, and complement normalization generally favored the 10 mg/kg dose. Trends toward clinically significant steroid reduction were present for both doses. Additionally, there appeared to be a greater dose response in subjects with high disease and serological activity. There was no apparent dose-response in the safety profile of belimumab with both doses being generally well-tolerated. These data supported the selection of 10 mg/kg belimumab as the marketed dose in general SLE, and also support its continued evaluation in combination with standard maintenance therapies in patients with WG or MPA.

The use of placebo in this trial is considered appropriate and does not put placebo patients at undue risk because all subjects in both the placebo group and the belimumab group will receive standard of care maintenance therapies for vasculitis (ie, azathioprine or methotrexate) and, if needed, subjects will receive appropriate rescue therapy in accordance with standard clinical practice as described above.

Induction and Maintenance Regimens for ANCA-Associated Vasculitis

Subjects participating in this trial will have had a moderate to severe episode of WG or MPA that was treated with high-dose corticosteroids (HDCS) and either RTX or CYC (IV or oral) to induce the remission of the disease. Subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR   Amend 03 04Feb14
- CYC 2mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

[*The cyclophosphamide dosing regimens are provided as targets but may be adjusted for older age, obesity, renal insufficiency, leukopenia, or other toxicities as dictated by local practice.*]   Amend 03 04Feb14

For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 0.5-1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ≤ 10 mg/day. As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.   Amend 03 04Feb14

Rituximab was approved in April 2011 by the FDA for the treatment of WG and MPA. It has been used in induction of remission in AAV for a number of years, (Gorman et al, 2003, Smith et al, 2006) and 2 recent trials published in 2010 (Stone et al, 2010), demonstrated non-inferiority to induction with cyclophosphamide, the latter of these trials being used as the basis for the recent US approval. The RTX dosing regimen of 4 infusions of 375 mg/m^2 each given 1 week apart reflects the dosing regimen that is approved by the FDA for this indication. An alternative RTX induction regimen (2 infusions of 1 gram each administered 2 weeks apart) is also offered in the protocol. Although the latter regimen is not licensed as an induction therapy for ANCA-vasculitis, it is very widely used in clinical practice and clinical evidence suggests that there is no difference between the two dosing regimens in terms of duration of B-cell depletion or therapeutic efficacy efficacy (Jones et al, 2009).

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Cyclophosphamide (2 mg/kg/day orally or IV 15 mg every 2 weeks for 3 doses and every 3 weeks thereafter) plus prednisone has been the standard induction regimen for WG and MPA since the early 1970s when initial work by Fauci and Wolff at the National Institutes of Health showed that this regimen induced disease remission in 12/14 patients and subsequent work showed that survival rates increased 80% using this regimen in what was previously an uniformly fatal disease (Fauci and Wolff, 1973; Fauci et al, 1983; Hoffman et al, 1992; Langford, 2011). Long term continued cyclophosphamide use, however, has been associated with significant toxicities (including infection, cystitis, cytopenias, and long term complications such as myelodysplasia and bladder cancer) and mortality (Langford, 2011).

A more recent study conducted by the European Vasculitis Group (Jayne et al, 2003) showed that after initial disease remission with cyclophosphamide and steroids, subjects could be switched to azathioprine (2 mg/kg/day) without having an increased risk of relapse compared to subjects whose remission was maintained using continued cyclophosphamide treatment. An induction regimen of CYC + prednisone followed by maintenance treatment with azathioprine is now considered the standard of care, given that administration of cyclophosphamide for longer durations does not offer an advantage from an efficacy standpoint and is associated with a greater potential for toxicity (Langford, 2011). The cyclophosphamide regimens described above are the same as those allowed in the inclusion criteria for this vasculitis study.

Once disease remission (defined as having, on 2 consecutive measurements at least 14 days apart: a BVAS v3 score of 0 and be receiving ≤ 10 mg/day of oral prednisone [or equivalent], between 6 and 26 weeks after the first dose of induction therapy) has been achieved, subject randomization into this protocol occurs. In this maintenance of remission trial, subjects will be randomized to receive a maintenance regimen of AZA (2 mg/kg/day) + placebo or AZA (2 mg/kg/day) + belimumab (10 mg/kg). Randomization in this protocol will be stratified by induction regimen.

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The primary safety population for the SLE indication, including 473 subjects who were taking azathioprine as a concomitant medication at baseline, provides a substantial amount of safety data to support the conduct of the proposed trial. For the maintenance of remission, azathioprine may be initiated as soon as it is clinically indicated following administration of

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induction therapy and no later than Day 0. For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset. Subjects naive to azathioprine and who experience azathioprine-related toxicity (Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT 2 times ULN, or a several gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting), following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience toxicities, a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis. The protocol instructs physicians to follow the appropriate local prescribing information for azathioprine or methotrexate (as applicable) prior to and during treatment.

Input on selection of these standard of care regimens was obtained from international experts in vasculitis, including members of the European Vasculitis Society (EUVAS) and the Vasculitis Clinical Research Consortium (VCRC), and consensus was reached that these regimens are appropriate for this international trial.

Complete details regarding the use of concurrent medications can be found in Section 5.5 of Protocol HGS1006-C1100.

Safety Considerations

An independent Data Monitoring Committee (DMC) will review safety data on an ongoing basis until the data are locked and analyzed (after which monitoring may be assumed by an internal HGS committee). The DMC will include at least 3 physicians and a statistician, none of whom are affiliated with the Sponsor. Belimumab has not yet been studied following use of IV cyclophosphamide (CYC) or rituximab (RTX); there is limited experience with the combination of belimumab and oral CYC. As an added safety precaution, initial randomization will be limited to 40 subjects per induction regimen (40 post-RTX induction and 40 post-CYC induction). The first DMC reviews will occur after the first 20 subjects per induction regimen (RTX or IV/oral CYC) have been randomized and have had a Week 8 visit. Once the first 20 subjects randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the DMC, who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with CYC. The DMC will review the data approximately every 6 months thereafter across both induction regimens. At all times the patients, study sites and sponsor will remain blinded to treatment allocation. Investigators and IRBs/IECs will be notified of the outcome of each DMC meeting.

The DMC will be notified of:

- all unexpected causally-related SAEs that are life-threatening or result in death;
- other unexpected causally-related SAEs;
- all reports of serious infections and opportunistic infections, irrespective of relationship to study agent; and
- subjects experiencing IgG < 250 mg/dL;

within protocol-specified timeframes. Based on these data, an ad hoc DMC meeting may be called at any time (see Section 8.3 of Protocol HGS1006-C1100 for additional detail regarding the DMC).

Based on the large body of safety data from SLE patients treated with belimumab and/or the mechanism of action of belimumab as a B cell immunosuppressant, anticipated potential risks of belimumab treatment in vasculitis patents include serious infusion and hypersensitivity reactions, infections, depression-related events, and malignancy. These risks are briefly reviewed here and are detailed more fully in the belimumab Investigator's Brochure. Both investigators and subjects will be appropriately informed regarding these risks. It is noted that because of the older patient population affected by this disease, the average age of subjects anticipated to participate in this study will be older than the average age of the SLE population studied to date (mean age of ~53 years at the time of diagnosis in vasculitis (Stone et al, 2010) compared with an average age of ~38 years in controlled Phase 3 studies of belimumab in SLE). As such, patients with vasculitis may be at a greater risk for infection than the SLE patients; however, the increased monitoring for infections by both the DMC (described above) and recommended to investigators (see below) will help to ensure subject safety through timely detection, treatment and reporting of infections.

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

In order to ensure subject safety with respect to infusion and hypersensitivity reactions, the protocol excludes patients with known history of allergic reactions to human or murine proteins or monoclonal antibodies. There is currently insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions to belimumab. The protocol recommends that based on clinical judgment, premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion. Antihistamine H2-receptor antagonists (eg, ranitidine) are also permitted.

Belimumab/placebo will be administered by investigators/site personnel prepared to manage infusion reactions and anaphylaxis. The infusion rate may be slowed or interrupted if the subject develops an infusion reaction. Investigators/site personnel should be aware of the risk of hypersensitivity reactions, which may present as infusion reaction, and monitor subjects closely. In the event of a serious reaction, belimumab/placebo administration must be discontinued immediately and the appropriate medical therapy administered. Per protocol, subjects are to remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase. 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. Beyond the first 2 infusions, subjects should be monitored during and for an appropriate period of time after infusion according to study sites' guidelines or standard operating procedure for IV infusions. Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

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Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in patients with SLE receiving immunosuppressant pharmacotherapy, including belimumab. Therefore, a diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The protocol requires that subjects should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy. If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

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The protocol recommends that subjects with persistent or worsening disease should receive appropriate rescue therapy in accordance with standard clinical practice, but if exceeding what is allowed per protocol, treatment with study agent (ie, belimumab or placebo) will be discontinued and the subject will be considered as having relapsed for the primary analysis. The list of prohibited medications that results in the subjects being considered as relapsed for the primary endpoint (Protocol Section 5.5.2.1), was developed because the need for the use of these agents (eg, RTX or CYC) is indicative of treatment failure (ie, disease relapse).

Moreover, concomitant use of such medications (eg, high-dose steroids) can be associated both with potent disease-modifying activity and/or significant toxicity that may introduce bias and confound interpretation of results. As such, no subject will be denied appropriate medical care for their condition due to their participation in this clinical study.

In addition, the Sponsor notes that although this is a placebo controlled trial, the sponsor does not consider that placebo patients are at undue risk because all subjects in both the placebo group and the belimumab group will receive standard of care maintenance therapies for vasculitis (ie, azathioprine or methotrexate) and, if needed, subjects will receive appropriate rescue therapy in accordance with standard clinical practice as described above.

Risk:Benefit Conclusions

In summary, the proposed Phase 3 study is a superiority study evaluating the safety and efficacy of belimumab for the maintenance of disease remission in patients with a clinical diagnosis of Wegener's granulomatosis or microscopic polyangiitis. The risk:benefit profile of 10 mg/kg IV belimumab in patients with active, autoantibody-positive SLE was demonstrated to be positive in the two Phase 3 SLE studies, thereby supporting its approval in Canada, the US, and the EU. Belimumab has already been shown to be effective in treating patients with active, autoantibody-positive SLE, a B cell mediated autoimmune disease. Like SLE, WG and MPA are also B cell mediated autoimmune diseases in which autoantibodies (in this case, against neutrophil components), are considered to be pathogenic (Popa et al, 1999). In each of these diseases, the general purpose of the therapy is similar – reducing disease activity by down regulating B cells (including autoreactive B cells) and reducing the level autoantibodies produced by those autoreactive B cell clones. Down regulating B cell numbers may also reduce inflammatory processes because of the role of B cells in antigen presentation. A limited amount of data from the IV Phase 3 studies suggests that belimumab may reduce vasculitic symptoms.

There are potential risks associated with belimumab treatment including serious infusion and hypersensitivity reactions, infections, depression-related events, and malignancy; however, in view of the serious and potentially life threatening nature of disease flares in WG and MPA, it is believed that the overall risk:benefit analysis for belimumab in the maintenance of remission in WG and MPA is favorable, especially in view of the nature of the trial as a superiority trial over a current standard of care regimen.

Appendix 13   Algorithm for Liver Chemistry Stopping and Follow-up Criteria

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Liver Stopping Event Algorithm
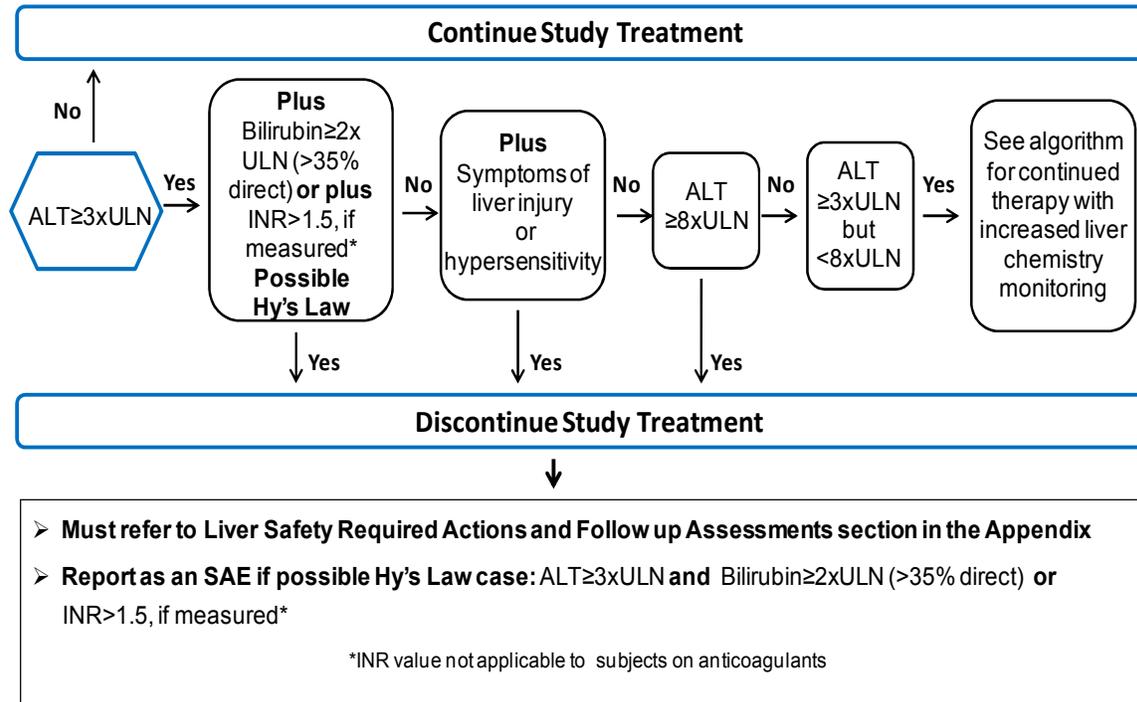
> - **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
> - **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*
>
> *INR value not applicable to subjects on anticoagulants

> - Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.5.2.1.

Liver Monitoring Event Algorithm with Continued Therapy for ALT≥3xULN but <8xULN
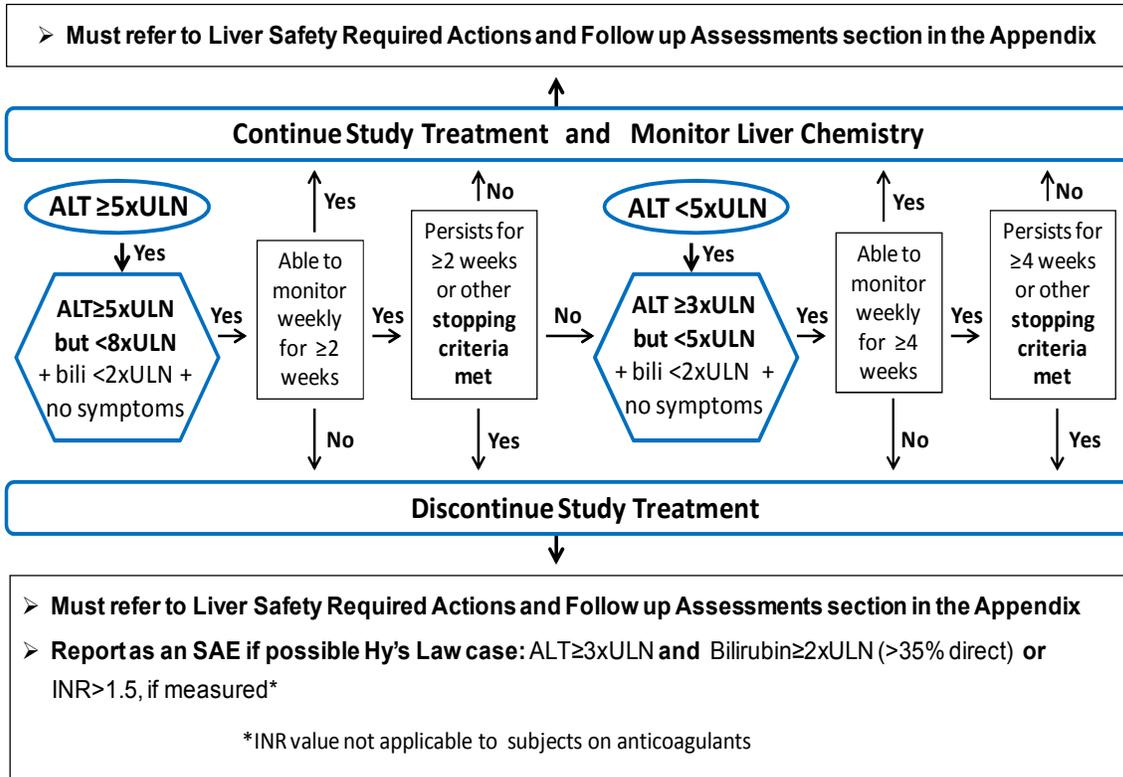
> Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.5.2.1.

References

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

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

Protocol Amendment 04, 26 February 2015
Protocol Number: HGS1006-C1100

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The proposed modifications to the protocol reflect a change by the sponsor to the strategic objectives for the evaluation of belimumab in ANCA-associated vasculitis (AAV). It is proposed that the trial should be changed from a Phase 3 study to allow for an exploratory evaluation of belimumab in AAV only. There is no longer the intention to seek a licensed indication for belimumab as an adjunctive maintenance therapy in AAV on the basis of the data emerging from this study. The term "Phase 3" has been removed from the study title.
   Enrolment of subjects onto the current trial has progressed at a much slower than expected rate. Based on current enrolment projections, data outputs from the current trial would unlikely be available for review until mid-2018.
   Having reviewed the timing of the study in the context of the evolving therapy area for ANCA-associated vasculitis, the sponsor feels that the current format and design of the BREVAS trial, if driven to completion as a Phase 3 investigation, would no longer provide significant and timely new information for the vasculitis community. On the basis of the BREVAS trial data alone, even in the event of a successful outcome, it is not felt that belimumab can be sufficiently well differentiated as a concomitant therapy for remission maintenance in AAV to fulfil a significant unmet need for patients where other therapeutic options are now available (e.g., rituximab).
   As such, GSK is proposing to modify the strategic objective of the trial such that it will be conducted as an exploratory study, in which global enrolment would be restricted to approximately 100 patients (compared to the original target of approximately 300). It is planned that the data will be published in descriptive format with exploratory analyses on efficacy endpoints undertaken as appropriate. It is expected that the safety data emerging from the smaller cohort of patients in BREVAS will contribute to our understanding of belimumab safety.
2. The study design and schedule has been modified throughout the protocol to clarify that the study will no longer be driven by the requirement to achieve at least 66 relapse events. The study will complete and the primary analysis will be undertaken once 12 months have elapsed following enrolment of the last subject.
3. The protocol has been modified throughout such that subjects completing the study will no longer have the option to participate in a 6-month open-label extension following completion of the double-blind treatment phase. The section entitled "open label extension phase" (6.4) and the related time and events table (Table 6-3) has been removed.
4. The study design schematics have been modified in the protocol by removal of the expected number of enrolled subjects; 'N=300-400' has been removed from the schematic.

5. In the statistical sections of the protocol, the sample size considerations have been modified to reflect the fact that approximately 100 patients will be recruited. The sample size is based largely on the feasibility of recruitment within a reasonable time-frame. Sample size calculations based on expected relapse rates have been removed from the protocol. The minimum detectable effect for a sample size of N=100 subjects has been determined.

    For the purposes of reporting the data, analysis of primary and secondary endpoints will be exploratory in nature. Nominal 'p' values may be reported and considered descriptive. Where appropriate point estimates and 95% confidence intervals will be constructed.

    The section on "Subgroup analyses" (7.5.2.1) has been removed as this is no longer considered relevant in the context of the smaller expected total sample size of approximately 100 subjects.

    In the section "Primary Efficacy Analysis" (8.5.2), we have clarified how stratification terms may be handled in the analysis if there are fewer than 5 events (relapses) in any of the stratification levels.

6. In the section "Dose, route of administration and schedule", we have clarified that the administration of belimumab/placebo should be over approximately one hour, but not less than one hour for reasons of safety.

7. The section on liver chemistry stopping and follow-up criteria, which describes how patient care should be managed if a liver event occurs during the study, has been updated with the most recent GSK-specified protocol for managing these events. The section also defines the circumstances and criteria that may allow a study treatment restart following a liver event. The section also includes the criteria for more intensive monitoring with continued therapy following a liver event. Accompanying figures have been placed in Appendix 13.

8. The adverse event reporting section (Section 7) has been modified throughout for consistency with AE, SAE or PSE data collection procedures and forms.

9. The text on progressive multifocal leukoencephalopathy (PML) has been updated to provide further guidance on the management of suspected cases.

10. The section "Reporting a pregnancy" has been modified to provide scope for following up the outcomes of a pregnancy (including premature termination) as well as the status of mother and child.

11. The section "Randomization procedure and assignment to treatment requirements" has been modified to remove the requirement for subjects to be randomised within 2 weeks of achieving remission. This corrects an error in the protocol and ensures consistency with wording across other sections of the protocol.

12. The reference list has been updated in the protocol.

13. Appendix 12 (Benefit-Risk assessment) has been updated to reflect the change in study status to an exploratory trial and to reflect the changes in the main protocol as outlined above.

Associated Protocol Modifications:

Protocol Cover Page

Change from:

Protocol Amendment: 03
Date: 04 February 2014

Change to:

Protocol Amendment 0**4**
Date: **26 February 2015**

Title of Study, Cover Page and Synopsis

Change from:

A ~~Phase 3,~~ Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Change to:

A Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Revision Chronology for HGS1006-C1100 (BEL115466)

Added rows:

	Date	**Document***
Local DNG2014N217970_01	**01 October 2014**	**Local Amendment 01 for France**
Local DNG2014N217970_02	**03 February 2015**	**Local Amendment 02for France**
Global DNG2013N167980_02	**26 February 2015**	**Amendment No 04**

Study Design and Schedule, Synopsis and Section 3.1, Basic Design Characteristics

Change from:

This is a ~~Phase 3~~, multi-center, multi-national, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

Change to:

This is a multi-center, multi-national, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

Change from:

Subjects will receive study agent (belimumab/placebo) plus AZA until ~~the results from the primary efficacy analysis are available~~ or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see below). The database will be locked and the primary analysis will be performed ~~after at least 66 subjects have experienced a relapse and at least~~ when 12 months have elapsed after the last subject is randomized.

Change to:

Subjects will receive study agent (belimumab/placebo) plus AZA until **the study has completed** or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see below). **The study will complete,** the database will be locked and the primary analysis will be performed **when** 12 months have elapsed after the last subject is randomized.

Study Design and Schedule, Synopsis

Deleted:

~~If top line data from the double-blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months and this will be supplied by the sponsor. After the 6-month open-label extension phase, subjects who wish to continue treatment may do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may continue to receive belimumab under a separate continuation~~

~~protocol. A separate informed consent will need to be provided for the continuation protocol.~~
~~The 8-week follow-up visit is not required for subjects entering the continuation protocol.~~

Schematic of study design, Synopsis and Section 3.1, Basic Design Characteristics

Change from:

Change to (removed number of subjects randomized from graphic):

Sample Size Considerations, Synopsis and Section 8.4, Sample Size Rationale

Deleted:

~~The relapse rate in the study is anticipated to be approximately 20% in the control group.~~
~~However, there is some uncertainty around this relapse event rate which could be 30% or~~

~~higher. This study is designed to target at least 66 subjects experiencing a relapse (as defined in the primary endpoint), which will provide 85% power to detect a reduction in relapse rates of 20 vs. 10% (hazard ratio = 0.472). With this same hazard ratio and a 30% event rate, a study with 66 subjects experiencing a relapse will provide 85% power to detect a reduction in the relapse rate from 30% to 15.5%. A target of 300 to 400 subjects will be randomized to achieve the required number of events.~~

~~After approximately 300 subjects have been randomized, the relapse rate in the overall population will be evaluated in a blinded manner internally by HGS while the enrollment continues. If the relapse rate is consistent with the 20% control rate assumption, enrollment will continue to 400 subjects to ensure timely accrual of the 66 events. However, if there is evidence that the relapse rate is higher than 20% control rate assumption, enrollment may be stopped at approximately 300 subjects. The primary efficacy analysis will be performed after at least 66 subjects have experienced a relapse and at least 12 months have elapsed after the last subject is randomized.~~

Added:

Approximately 100 subjects will be randomized. The sample size has been determined based on the feasibility of enrolling patients into the study within a reasonable time-frame. The sample size was not based on statistical considerations and the analysis of primary and secondary endpoints will be exploratory in nature. The primary efficacy analysis will be performed after 12 months have elapsed following randomization of the last subject.

Although the sample size is based on feasibility, the minimal detectable effect has been determined. Assuming an observed relapse rate at 18 months of 20% in the placebo group, a relapse rate of ≤7.0% on belimumab (hazard ratio ≤0.32) would be statistically significant (p<0.05) in a study of 100 subjects (50 per arm).

Analysis of Primary Efficacy Endpoint, Synopsis

Change from:

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The primary efficacy analysis will be performed after ~~at least 66 subjects have experienced a relapse~~ and at least 12 months have elapsed ~~after the last subject is randomized~~.

Change to:

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The primary efficacy analysis will be performed after 12 months have elapsed **following randomization of the last subject**.

Analysis of Major Secondary Efficacy Endpoints, Synopsis

Deleted:

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

Section 3.1, Basic Design Characteristics

Deleted:

~~If the result on the primary efficacy endpoint from the double-blind portion of this trial shows that belimumab is superior to placebo, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months and this will be supplied by the sponsor. After the 6-month open-label extension phase, subjects who wish to continue treatment may do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may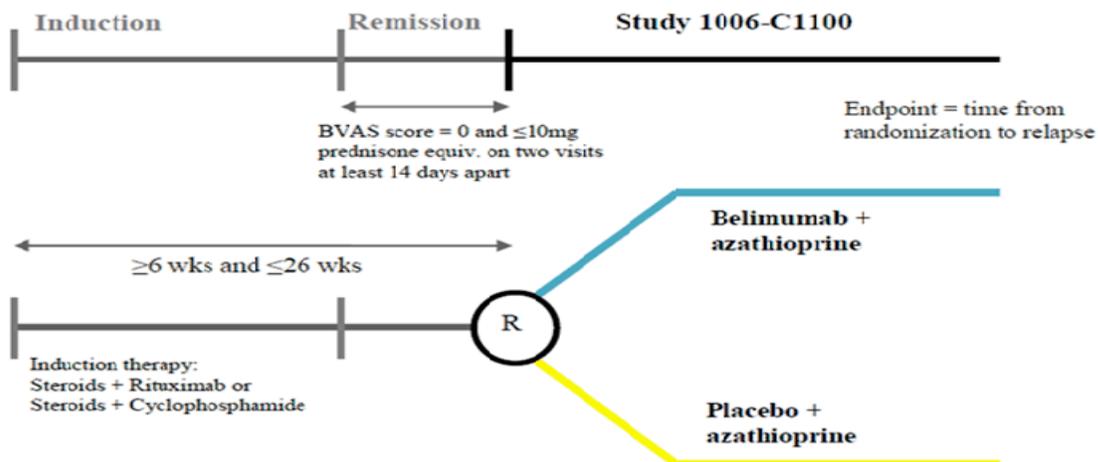 continue to receive belimumab under a separate continuation protocol. A separate informed consent will need to be provided for the continuation protocol. The 8 week follow-up visit is not required for subjects entering the continuation protocol.~~

Section 5.3 Dose, Route of Administration, and Schedule

Change from:

The treatment groups include one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving azathioprine (as described in Section 5.5.3). Belimumab/placebo will be administered intravenously over 1 hour. Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days thereafter. ~~Following the final double-blind visit, eligible subjects (see Section 6.4) will have the option to continue in the 6-month open-label extension period.~~

Change to:

The treatment groups include one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving azathioprine (as described in Section 5.5.3). Belimumab/placebo will be administered intravenously over 1 hour. **The intent of this instruction is to prevent more rapid infusion of belimumab which may result in a higher incidence of infusion reactions. Infusion time need <u>not</u> be exactly one hour as it is often difficult to so precisely adjust infusion times and there may be clinical reasons for infusions lasting longer than one hour. Therefore, the instruction should be interpreted as infusion over <u>at least</u> one hour. The target infusion time should still be approximately**

one hour assuming no other issues intervene. Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days thereafter.

Change from:

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase ~~and the open-label extension.~~

Change to:

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase.

Section 6.3 Double-Blind Treatment Phase

Change from:

Subjects who have not experienced a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1) will remain on double-blind treatment with study agent until ~~top line data from the primary analysis are available. If top line data from the double-blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who received treatment with study agent until completion of the double-blind treatment period and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the 6-month open-label extension phase.~~

Subjects ~~who do not enter the open-label extension,~~ will return for an Exit visit (approximately 4 weeks after the last dose of study agent), and a follow-up visit (approximately 8 weeks after the last dose of study agent).

Change to:

Subjects who have not experienced a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1) will remain on double-blind treatment with study agent until **the study has completed. The study will complete and the primary efficacy analysis will be performed when 12 months have elapsed following randomization of the last subject.**

Subjects will return for an Exit visit (approximately 4 weeks after the last dose of study agent), and a follow-up visit (approximately 8 weeks after the last dose of study agent).

Table 6-1 Footnotes:

Change from:

11. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 4 weeks after the last dose of study agent). The Exit Visit should ~~only~~ be completed for subjects who discontinue the double blind treatment phase early or ~~for~~ subjects ~~that~~ have ~~successfully~~ completed the double-blind treatment phase ~~and do not wish to participate in the open label extension phase~~. Subjects who discontinue treatment but have not relapsed will remain on the double blind study visit schedule. ~~For subjects who complete the double blind phase and enter the open label phase, refer to Table 6-3 for visit details.~~

Change to:

11. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 4 weeks after the last dose of study agent). The Exit Visit should be completed for subjects who discontinue the double blind treatment phase early or **when** subjects have completed the double-blind treatment phase. Subjects who discontinue treatment but have not relapsed will remain on the double blind study visit schedule.

Change from:

13. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent ~~for subjects withdrawing early and those subjects who do not continue in the 6 month open-label extension phase.~~

Change to:

13. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent.

Table 6-2 Footnotes

Change from:

7. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 1-4 weeks after the last dose of study agent). The Exit Visit should ~~only~~ be completed for subjects who discontinue the double blind treatment phase early or ~~for~~ subjects ~~that~~ have ~~successfully~~ completed the double-blind treatment phase ~~and do not wish to participate in the open label extension phase. For subjects who complete the double blind phase and enter the open label phase, refer to Table 6-3 for visit details~~.

Change to:

7. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 1-4 weeks after the last dose of study agent). The Exit Visit should be completed for subjects who discontinue the double blind treatment phase early or **when** subjects have completed the double-blind treatment phase.

Change from:

9. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent ~~for subjects withdrawing early and those subjects who do not continue in the 6 month open-label extension phase~~.

Change to:

9. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent.

Deleted: Section 6.4 "Open-Label Extension Phase" has been deleted and all subsequent sections have been renumbered accordingly.

~~6.4 Open-Label Extension Phase~~

~~In the 6-month open-label extension, all subjects will receive 10 mg/kg belimumab every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the last dose). The first dose on the open-label extension will be given 4 weeks after completion of the double-blind period. Day 0 is the first visit in the extension phase of the trial and represents the first belimumab administration for placebo subjects. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.~~

~~All subjects participating in the open-label extension will continue to be monitored for efficacy and safety as per the study calendar (see Table 6-3).~~

~~During the 6-month open-label extension, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate. Prohibited medications during this phase are live vaccines, biological therapies and other investigational agents.~~

~~All subjects will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent. These visits apply to subjects who have completed as well as those who have withdrawn early from the open-label extension.~~

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

Deleted:
Table 6-3 Open Label Extension Phase and all associated footnotes have been deleted *and the subsequent table has been renumbered accordingly.*

Section 6 Study Procedures

Change from:

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

Change to:

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

Section 6.5 Laboratory Tests

Change from:

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

Change to:

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

Section 6.6.2 Phase III-IV Liver Chemistry Stopping and Follow-up Criteria

The section "Phase III-IV Liver Chemistry Stopping and Follow-up Criteria" has been deleted. The deleted text is not shown here. The section has been replaced by the following sections (6.5.2-6.5.3) and text:

6.5.2 Liver Chemistry Stopping and Follow-up Criteria

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

Liver Chemistry Stopping Criteria- Liver Stopping Event	
ALT-absolute	ALT $\geq$ 8xULN
ALT Increase	ALT $\geq$ 5xULN but <8xULN persists for $\geq$2 weeks
	ALT $\geq$ 3xULN but <5xULN persists for $\geq$4 weeks
Bilirubin[1, 2]	ALT $\geq$ 3xULN and bilirubin $\geq$ 2xULN (>35% direct bilirubin)
INR[2]	ALT $\geq$ 3xULN and INR>1.5, if INR measured
Cannot Monitor	ALT $\geq$ 5xULN but <8xULN and cannot be monitored weekly for $\geq$2 weeks
	ALT $\geq$ 3xULN but <5xULN and cannot be monitored weekly for $\geq$4 weeks
Symptomatic[3]	ALT $\geq$ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
1) Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT $\geq$ 3xULN **and** bilirubin $\geq$ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.	
2) All events of ALT $\geq$ 3xULN **and** bilirubin $\geq$ 2xULN (>35% direct bilirubin) or ALT $\geq$ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.	
3) New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).	

6.5.2.1 Required Actions and Follow up Assessments following ANY Liver Stopping Event

ACTIONS:

- Immediately discontinue study treatment

- Report the event to GSK **within 24 hours**

- Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE (All events of ALT $\geq$ 3xULN and bilirubin $\geq$ 2xULN (>35% direct bilirubin) or ALT $\geq$ 3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants)

- Perform liver event follow up assessments

- Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below)

Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 13).

MONITORING

> **For bilirubin or INR criteria:**
> - Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours**
>
> - Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline
>
> - A specialist or hepatology consultation is recommended
>
> **For All other criteria:**
> - Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours**

Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline

FOLLOW UP ASSESSMENTS

- Viral hepatitis serology (includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody)

- Blood sample for pharmacokinetic (PK) analysis, obtained within approximately one to two weeks after last dose (PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Fractionate bilirubin, if total bilirubin≥2xULN

- Obtain complete blood count with differential to assess eosinophilia

- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form

- Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications

- Record alcohol use on the liver event alcohol intake case report form

For bilirubin or INR criteria:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).

- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).

Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

6.5.3 Increased Monitoring Criteria with Continued Therapy

If met see required actions below:
- If ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks OR

- ALT ≥3xULN **and** <5xULN and bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks

6.5.3.1 Required Actions and Follow Up Assessments for Increased Monitoring with Continued Therapy
- Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety.

- Subject can continue study treatment

- Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline

- If at any time subject meets the liver chemistry stopping criteria, proceed as described above for Required Actions and Follow up Assessments following ANY Liver Stopping Event

- If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly.

- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

Added:

6.5.4 Study Treatment Restart

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than drug induced liver injury [DILI]) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there

should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).

- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an HLA genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.

- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.

- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.

- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.

- Study treatment must be administered at the dose specified by GSK.

- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.

- GSK to be notified of any adverse events, as per Section 7.2

Section 6.6 Exit Visit

Change from:

Refer to the Study Calendar (Table 6-1, Table 6-2 and ~~Table 6-3~~) for a list of procedures required at this visit.

Change to:

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

Section 6.7 8-Week Follow-up Visit

Change from:

All subjects must return for a follow-up visit approximately 8 weeks after the last dose of study agent, ~~unless entering the long-term continuation protocol~~.

Refer to the Study Calendar (Table 6-1, Table 6-2 and ~~Table 6-3~~) for a list of procedures required at this visit.

Change to:

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

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

Section 7 Adverse Event Reporting

Added:

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

Section 7.1 Definitions

Change from:

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

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

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

~~*An inpatient hospitalization is defined as an admission for any length of time. A hospitalization for administration of study agent, for routine or planned clinical procedures, or~~

~~for "social" reasons (not the result of any adverse change in the subject's condition) should not be considered an adverse event and should not be reported as a serious adverse event. If the subject experiences any adverse change in condition during hospitalization, the condition must be reported as an adverse event or serious adverse event according to the above definitions.~~

~~[+]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above (eg, possible drug-induced liver injury). These should also usually be considered serious. (ICH guidelines, March 1995)~~

~~**UNEXPECTED ADVERSE EVENT:** An adverse event, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Expected means the event has previously been observed with the study agent and is identified and/or described in the applicable product information. It does not mean that the event is expected with the underlying disease(s) or concomitant medications.~~

Change to:

ADVERSE EVENT

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

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

Events meeting the definition of an AE include:

- **Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition**

- **New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study**

- **Signs, symptoms, or the clinical sequelae of a suspected interaction**

- **Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.**

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

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

- **Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE**

- **Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)**

- **Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen**

- **The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition**

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

 a. **Results in death**
 b. **Is life-threatening**
 c. **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.**
 d. **Requires hospitalisation or prolongation of existing hospitalisation**
 e. **NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.**
 f. **Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.**
 g. **Results in disability/incapacity, or**
 h. **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.**
 i. **Is a congenital anomaly/birth defect**

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

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

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

Section 7.2 Reporting Adverse Events to the Sponsor

Change from:

Serious Adverse Events (SAEs) must ALSO be recorded on the SAE ~~Worksheet and sent to the HGS Drug Safety designee~~ within 24 hours of site personnel becoming aware of the SAE, regardless of expectedness. All ~~pages~~ of the SAE ~~Worksheet~~ should be completed, but ~~the SAE Worksheet~~ should not be held until all information is available. ~~Additional~~ information and corrections should be ~~provided on subsequent SAE Worksheets~~ as described in the Study Procedures Manual. ~~SAE Worksheets should be sent either via the EDC system, if SAE EDC functionality is available or by facsimile to the HGS Drug Safety designee using the fax number listed on the SAE Worksheet~~.

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

SAEs that occur off study, after the follow-up period, that are assessed by the investigator as definitely, possibly or probably related to study agent must be reported to the ~~Drug Safety designee on the SAE worksheet. Post study SAEs will not be documented on the AE eCRF.~~

Change to:

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

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

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

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

Change from:

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

Change to:

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

Section 7.4 Laboratory Abnormalities as Adverse Events

Change from:

~~A laboratory abnormality should be reported as an adverse event if it is associated with an intervention. Intervention includes, but is not limited to, discontinuation of treatment, dose reduction/delay, or concomitant therapy. In addition, any medically important laboratory abnormality may be reported as an adverse event at the discretion of the investigator. This includes laboratory abnormalities for which there is no intervention but the abnormal value(s) suggests a disease or organ toxicity.~~ If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine RBC increased). In

addition, an IgG abnormality < 250 mg/dL (Grade 4) should be recorded ~~as an adverse event (and SAE if meeting the criteria in Section 7.1)~~.

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

Change to:

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

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

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

Section 7.5 Progressive Multifocal Leukoencephalopathy

Change from:

If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.

Change to:

If PML is confirmed, study agent should be discontinued and consideration should be given to stopping **all** immunosuppressant therapy.

Section 7.7 Reporting a Pregnancy

Change from:

~~Pregnancies must be reported to the HGS Drug Safety designee within 24 hours of the site becoming aware of a pregnancy in a study subject. All pregnancies that are identified from the start of study agent through 16 weeks following the last dose of study agent should be reported. All pregnancies are tracked up to term or delivery following the last study agent treatment. When pregnancy is reported, HGS Drug Safety sends an acknowledgement memorandum to the principal investigator along with a Pregnancy Assessment Form. A Pregnancy Assessment Form must be completed every three months until live birth, elective termination of the pregnancy, or miscarriage. The site is responsible for following the subject's pregnancy to final outcome.~~

~~Pregnancies are not considered adverse events. Complications or medical problems associated with a pregnancy are considered AEs and may be SAEs. Complications or medical problems are reported as AEs/SAEs according to the procedure described in Section 7.1 and Section 7.2.~~

Change to:

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to the Sponsor within 2 weeks of learning of its occurrence. All pregnancies that are identified from the start of study agent through 16 weeks following the last dose of study agent should be reported. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

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

Section 7.8 Investigator Evaluation of Adverse Events

Change from:

The investigator will evaluate all adverse events with respect to seriousness, severity (intensity ~~or grade~~), and causality (relationship to study agent). ~~The criteria for serious are listed in Section 7.1. The severity of an AE is to be evaluated according to the Adverse Event Severity Grading Tables in Appendix 7. If an AE does not have Adverse Event Severity Grading in Appendix 7, the following severity classifications will be used~~:

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SEVERITY:

~~Grade 1~~ **Mild**   ~~- causing no limitation of usual activities.~~
~~Grade 2~~ **Moderate**   ~~- causing some limitation of usual activities.~~
~~Grade 3~~ **Severe**   ~~- causing inability to carry out usual activities.~~
~~Grade 4~~ **Life-threatening***   ~~- potentially life-threatening or disabling; significant medical~~
~~intervention is required.~~

~~*Note — a severity assessment of Life-threatening is not necessarily the same as the seriousness criterion of Life-threatening (see "serious" criteria Section 7.1). The former means that the event is a potential threat. The latter means that the event is an immediate threat to life.~~

CAUSALITY:

~~It is a regulatory requirement for investigators~~ to assess relationship between the ~~investigational product(s)~~ and the occurrence of each AE/SAE based on the information available. ~~The assessment should be reviewed on receipt of any new information and amended if necessary.~~ A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. ~~Facts/evidence or arguments that may support a "reasonable possibility" include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.~~

Change to:

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

SEVERITY:

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

- Moderate   **An event that is sufficiently discomforting to interfere with everyday activities (Grade 2 DMID).**

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

- **Not applicable** **Those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).**

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as

severe. An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

CAUSALITY:

The investigator is obligated to assess the relationship between **study treatment** and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. **The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.**

For each AE/SAE the investigator <u>must</u> document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Section 7.9 Follow-up of Adverse Events

Change from:

~~Adverse events~~ that occur from the start of study medication through 8 weeks after the date of last administration of study agent are ~~followed until final outcome is known or until the end of the 8-week study follow-up period. Adverse events that have not resolved at the end of the 8-week study follow-up visit are recorded on the adverse event case report form (AE eCRF) as ONGOING.~~

~~SAEs that have not resolved by the end of the follow-up period are followed until final outcome of recovered or recovered with sequelae is achieved. If it is not possible to obtain a final outcome for an SAE (eg, the subject is lost to follow-up), the reason a final outcome could not be obtained will be documented by the investigator~~.

Change to:

Serious and non-serious adverse events that occur from the start of study medication **administration** through 8 weeks after the date of last administration of study agent are **reported.**

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

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

Section 8.1 General Statistical Considerations

Change from:

The database will be locked for the primary analysis after all data have been collected, verified and validated for all subjects through 12 months after the randomization of the last subject or when 66 events (relapse as defined for the primary efficacy endpoint) have been observed, whichever is later. All subjects and study site personnel will remain blinded to original treatment assignment until after the final database is locked and the results of the study are made publicly available.

For the analysis of the primary and the major secondary efficacy endpoint, a step-down sequential testing procedure will be used to control the overall type 1 error. With this procedure, the primary endpoint (time to the first relapse) will be evaluated first. If the primary efficacy endpoint demonstrates statistical significance (2-sided, alpha=0.05) then inference will proceed to the major secondary efficacy endpoint, time to the first major relapse (2-sided, alpha = 0.05). If the result is statistically significant, superiority of belimumab on the time to the first major relapse will be established. If statistical significance is not met, p values may be reported and considered descriptive.

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

Change to:

The database will be locked for the primary analysis after all data have been collected, verified and validated for all subjects through 12 months after the randomization of the last subject. All subjects and study site personnel will remain blinded to original treatment assignment until after the final database is locked and the results of the study are made publicly available.

Analysis of primary and secondary endpoints will be exploratory in nature. Nominal p values may be reported and considered descriptive. **Where appropriate point estimates and 95% confidence intervals will be constructed.**

Section 8.2 Randomization Procedure and Assignment to Treatment Groups

Change from:

This is a ~~Phase 3,~~ multi-center, multinational, randomized, double-blind, placebo-controlled study. Once subjects have consented, have undergone all screening procedures and have been determined to be eligible for the study, they will be randomly assigned (via an interactive web response system [IWRS]) to 1 of 2 treatment groups (belimumab [10 mg/kg] or placebo) in a 1:1 ratio. At randomization, subjects will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. RTX). Randomization will be performed on Day 0. ~~Day 0 (first administration of belimumab/placebo and azathioprine) must occur no more than 2 weeks after confirmation of remission.~~

Change to:

This is a, multi-center, multinational, randomized, double-blind, placebo-controlled study. Once subjects have consented, have undergone all screening procedures and have been determined to be eligible for the study, they will be randomly assigned (via an interactive web response system [IWRS]) to 1 of 2 treatment groups (belimumab [10 mg/kg] or placebo) in a 1:1 ratio. At randomization, subjects will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. RTX). Randomization will be performed on Day 0.

Section 8.5.2 Primary Efficacy Analysis

Change from:

The primary efficacy analysis will compare the time to first relapse from Day 0 between the placebo/azathioprine group and the belimumab/azathioprine combination group using a Cox proportional hazard model, adjusted for ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide). However, the adjustment of induction regimen will be changed to rituximab vs. IV and/or oral cyclophosphamide if the number of events (relapse) is less 5 in subjects using the oral or IV cyclophosphamide. For any subject who does not experience a relapse, the time to first relapse will be censored at the time of the subject's last assessment. Subjects who discontinue study agent prior to relapse/flare (as defined in primary efficacy endpoint) are to be followed per protocol for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The database will be locked and the primary efficacy analysis will be performed after ~~at least 66 subjects have experienced a relapse and at least~~ 12 months have elapsed after the last subject is randomized.

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Change to:

The primary efficacy analysis will compare the time to first relapse from Day 0 between the placebo/azathioprine group and the belimumab/azathioprine combination group using a Cox proportional hazard model, adjusted for ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide). However, the adjustment of induction regimen will be changed to rituximab vs. IV and/or oral cyclophosphamide if the number of events (relapse) is less **than** 5 in subjects using the oral or IV cyclophosphamide. **If there are then still less than 5 patients with an event (relapse) in any of the levels of this or any other stratification factor then the stratification term may be removed from the model.** For any subject who does not experience a relapse, the time to first relapse will be censored at the time of the subject's last assessment. Subjects who discontinue study agent prior to relapse/flare (as defined in primary efficacy endpoint) are to be followed per protocol for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The database will be locked and the primary efficacy analysis will be performed after 12 months have elapsed **following randomization of the last subject.**

Deleted:

~~**Section 8.5.2.1 Subgroup Analysis**~~

~~Subgroup analysis, of the primary efficacy endpoint only, will be performed in the following subgroups:~~

- ~~ANCA type (anti-PR3 vs. anti-MPO)~~
- ~~Disease type (WG vs. MPA)~~
- ~~Disease stage at induction (initial diagnosis vs. relapsing disease)~~
- ~~Induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide)~~
- ~~Race (white, American Indian, Asian, and black)~~
- ~~Region (US/Canada, EU/Australia/Israel, Americas excluding US/Canada, and Asia)~~
- ~~Age (< 65 vs. ≥ 65)~~
- ~~Gender~~
- ~~Duration of IV corticosteroid pulse used for induction (1 day vs > 1 day)~~

Section 8.5.5 Major Secondary Endpoint analysis and Other Efficacy Analyses

Change from:
The analysis of the major secondary efficacy endpoint will be performed using the same method described for the primary efficacy endpoint, but censoring subjects who receive any prohibited medication (as defined in Section 5.5.1) prior to an observation of any major BVAS item. Any censoring will be applied on the date prohibited medications are received.

Change to:

The **exploratory** analysis of the major secondary efficacy endpoint will be performed using the same method described for the primary efficacy endpoint, but censoring subjects who receive any prohibited medication (as defined in Section 5.5.1) prior to an observation of any major BVAS item. Any censoring will be applied on the date prohibited medications are received.

References

Added:

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, Study Overview and Patient Population

Change from:

This is a ~~Phase 3,~~ multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

Change to:

This is a multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

Change from:

~~A target of 300 to 400 subjects~~ who are between 6 and 26 weeks from starting induction therapy, achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving ≤10 mg/day prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart will be enrolled into the study.

Change to:

Approximately 100 subjects with ANCA-vasculitis who are between 6 and 26 weeks from starting induction therapy, **who** achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving ≤10 mg/day prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart will be enrolled into the study.

Change from:

The database will be locked and the primary analysis will be performed ~~after at least 66 subjects have experienced a relapse and at least~~ 12 months have elapsed after the last subject is randomized.

Change to:

The database will be locked and the primary analysis will be performed **when** 12 months have elapsed after the last subject is randomized.

Deleted:

~~If top-line data from the double-blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in a 6-month open-label extension period, in which all subjects will receive 10 mg/kg belimumab IV. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety.~~

Deleted:

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

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

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, Safety Considerations

Change from:

Per protocol, subjects are to remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase ~~and the open-label extension~~.

Change to:

Per protocol, subjects are to remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase.

Appendix 13 Algorithm for Liver Chemistry Stopping and Follow-up Criteria

Added:

Liver Stopping Event Algorithm

Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.5.2.1.

References

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

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

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

Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.5.2.1.

Deleted:

Phase III-IV Liver Safety Algorithms

ALT≥3xULN

Yes → plus bilirubin ≥2x ULN (>35% direct) (or **plus** INR >1.5, if measured)*

No → Hepatitis symptoms or rash?

No → ALT ≥8xULN

No → ALT ≥5xULN but <8xULN

Yes → Able to monitor weekly for ≥ 2 wks?

Yes → ALT ≥5 and <8xULN for ≥ 2 wks

No → Able to monitor weekly for 4 weeks?

Yes → ALT≥3xULN but <5xULN + bilirubin <2xULN+no symptoms

Continue IP Obtain twice monthly liver chemistries until normalised or back to baseline values ← Yes — ALT<3xULN + bilirubin <2xULN after ≤ 4 wks? ← Notify GSK within 24h to discuss subject safety; continue IP; check liver chemistry weekly for 4 weeks

No / No** / No

Yes (from Hepatitis symptoms or rash / ALT ≥8xULN):

• Instruct subject to stop investigational product (IP)
• Notify GSK and arrange clinical followup within 24h
• Perform liver chemistries and liver event follow up assessments (serology, PK sample etc as in protocol)
• Report as SAE (excl. hepatic impairment or cirrhosis studies) and complete liver event CRF, SAE data collection tool, and liver imaging and/or biopsy CRFs if tests performed.
• Obtain twice weekly liver chemistries until resolved, stabilised or returned to baseline values
• Consultation with hepatologist/specialist recommended
• **Withdraw subject from study after monitoring complete unless protocol has option to restart drug**

No (from monitoring boxes):

• Instruct subject to stop investigational product (IP)
• Notify GSK within 24h and arrange clinical followup within 24-72h
• Perform liver chemistries and liver event follow up assessments (serology, PK sample etc as in protocol)
• Complete liver event CRF, SAE data collection tool if appropriate, and liver imaging and/or biopsy CRFs if tests performed.
• Obtain weekly liver chemistries [**as far as possible in these subjects] until resolved, stabilised or returned to baseline
• **Withdraw subject from study after monitoring complete unless protocol has option to restart drug**

*INR value not applicable to subjects on anticoagulants

Protocol Amendment 03, 04 February 2014
Protocol Number: HGS1006-C1100

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The protocol has been modified to provide flexibility in timing of initiation of azathioprine maintenance therapy i.e., option to initiate as soon as clinically indicated and prior to confirmation of remission.
2. The protocol has been modified to allow alternative unlicensed rituximab dose for induction (1 g every 2 weeks) in addition to the licensed dosing regimen (375 mg/m^2/wk for 4 doses).
3. The protocol has been modified to provide flexibility in timing of baseline BVAS assessments – allowing 2 baseline assessments separated by at least 14 days (instead of strict 21-35 days separation).
4. The absolute requirement to randomize within 14 days of confirmation of remission has been removed and clarification has been added that subjects cannot be randomized until at least 6 weeks after initiation of induction therapy.
5. A study schematic diagram has been added to clarify the trial design.
6. Clarification has been added regarding 'high dose corticosteroids' for induction and text provides guidance but allows locally accepted practice. No subject should receive <10mg for induction.
7. The protocol has been modified to allow some flexibility to cyclophosphamide dosing regimens (allows adjustment for age, obesity, renal insufficiency, leukopenia, other toxicities) for induction.
8. The protocol has been modified to allow the option to use methotrexate from the outset, as an alternative to azathioprine, if patient is a priori known to be azathioprine intolerant or has low/absent thiopurine methyltransferase (TPMT) activity. Exclusion of subject with intolerance or contraindications to methotrexate (where this is being considered as an alternative to azathioprine).
9. The protocol has been modified to allow equal to/less than 10 mg prednisone daily during maintenance (rather than strictly <10 mg prednisone daily); articulated option to taper as clinically appropriate.
10. Progressive multifocal leukoencephalopathy text has been updated based on new information. This addition is to ensure full awareness of PML risk in the trial population and to provide clarification on clinical assessment and actions.
11. In Appendices 1 and 2, "criteria" in the title and text has been changed to "definition". The List of Appendices has been updated accordingly.
12. Appendix 5 has been updated to include a sample of the VDI case report form.
13. The Benefit and Risk Assessment section has been updated to reflect new and/or amended information in the protocol body.

14. Minor administrative change was made for bulleted presentation in Benefit and Risk Assessment. These minor changes are not shown in the Modifications section below.
15. The list of abbreviations has been updated to add abbreviations as a result of new and/or amended text and to correct previous errors.

Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment 02
Date: 25 April 2013

Modified to:

Protocol Amendment 0**3**
Date: **04 February 2014**

Revision Chronology for HGS1006-C1100 (BEL115466)

Added row:

	Date	Document*
Global DNG2013N167980_01	**04 February 2014**	**Amendment No 03**

Synopsis, Diagnosis & Inclusion Criteria
Section 4.1, Inclusion Criteria

Formerly:
3. In the 26 weeks prior to randomization (Day 0), had an episode of moderately to severely active WG or MPA requiring treatment under one of the following induction regimens:

  – A single course of rituximab administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
  – cyclophosphamide 2 mg/kg/day orally plus HDCS OR
  – cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

5. Have a Birmingham Vasculitis Activity Score (BVAS v.3 [Appendix 3]) of 0 and be receiving ≤ 10 mg/day oral prednisone (or equivalent) on 2 consecutive measurements 21 to 35 days apart, achieved no more than 26 weeks after the first dose of induction therapy (either

CYC or RTX, as defined in Section 3.1). ~~Maintenance therapy (belimumab/placebo + azathioprine) must start no more than 2 weeks after confirmation of remission~~.

Modified to:

3. In the 26 weeks prior to randomization (Day 0), had an episode of moderately to severely active WG or MPA requiring treatment under one of the following induction regimens:

- A single course of rituximab administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- **A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR**
- cyclophosphamide 2 mg/kg/day orally plus HDCS OR
- cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

5. Have a Birmingham Vasculitis Activity Score (BVAS v.3 [Appendix 3]) of 0 and be receiving ≤ 10 mg/day oral prednisone (or equivalent) on 2 consecutive measurements **at least 14** days apart, **between 6 and** 26 weeks after the first dose of induction therapy (either CYC or RTX, as defined in Section 3.1). **A minimum 6 week period should elapse between initiation of induction therapy and randomization.**

Synopsis, Exclusion Criteria and Section 4.2, Exclusion Criteria

Formerly:

2.   Known intolerance to azathioprine (AZA) ~~or in whom AZA is contraindicated~~.

Modified to:

2.   Known intolerance **or contraindications** to azathioprine (AZA); **and known intolerance or contraindications to methotrexate where methotrexate is being considered as an alternative to AZA for maintenance therapy.**

Synopsis, Section Study Design and Schedule and Section 3.1 Basic Design Characteristics

Formerly:

Subjects enrolled into the trial must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either cyclophosphamide (CYC) or rituximab (ie, induction therapy) in the 6 months leading up to randomization. Subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course rituximab (RTX) administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- Cyclophosphamide 2mg/kg/day orally plus HDCS OR
- Cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The ~~doses of~~ cyclophosphamide are ~~given~~ as targets but may be adjusted for renal insufficiency or ~~white cell counts~~ as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach < ~~10~~ mg/day.

Subjects who are ~~within~~ 26 weeks of starting induction therapy, achieve a BVAS v.3 score of 0 (Appendix 4), and are receiving < ~~10~~ mg/day prednisone (or equivalent) on 2 consecutive measurements ~~21 to 35~~ days apart may be enrolled into the study. Randomization will be performed on Day 0. ~~Day 0 (first administration of belimumab/placebo) must occur no more than 2 weeks after confirmation of remission. Azathioprine must be initiated at any time following confirmation of remission up to and including Day 0.~~ All subjects ~~will~~ be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). Belimumab or placebo will be supplied by the sponsor during this double-blind treatment phase. It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, 28, and every 28 days thereafter.

Modified to:

Subjects enrolled into the trial must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either cyclophosphamide (CYC) or rituximab (ie, induction therapy) in the 6 months leading up to randomization. Subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course rituximab (RTX) administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- **A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR**
- Cyclophosphamide 2mg/kg/day orally plus HDCS OR
- Cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

*[The cyclophosphamide **dosing regimens** are **provided** as targets but may be adjusted for **older age, obesity,** renal insufficiency, **leukopenia, or other toxicities** as dictated by local practice.]*

For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by **0.5-**1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach **≤ 10** mg/day. **As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.**

Subjects who are **between 6 and** 26 weeks of starting induction therapy, achieve a BVAS v.3 score of 0 (Appendix 4), and are receiving **≤ 10** mg/day prednisone (or equivalent) on 2 consecutive measurements **at least 14** days apart may be enrolled into the study. **A minimum 6 week period should elapse between initiation of induction therapy and randomization.** Randomization will be performed on Day 0. **A schematic of the study design is shown below/in Figure 1.**

All **randomized** subjects **should** be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. **Azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine should not be initiated any later than Day 0.** Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). Belimumab or placebo will be supplied by the sponsor during this double-blind treatment phase. It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, 28, and every 28 days thereafter.

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Added:

Schematic of Study Design/Figure 1 Schematic of Study Design

Section List of Abbreviations

Formerly:

CRO   Contract ~~Reseach~~ Organization
WG   Wegener's Granulmatosis

Modified to:

CRO   Contract **Research** Organization
WG   Wegener's Granulmatosis **(Granulomatosis with polyangiitis)**

Added:

TPMT   **thiopurine methyltransferase**

Section 1.1 Disease Background, 2nd sentence

Formerly:

A subset of the primary small vessel vasculitides: Wegener's granulomatosis, also **known** as granulomatosis with polyangiitis (GPA), microscopic polyangiitis and Churg-Strauss syndrome (CSS), are characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) (Jennette and Falk, 1997).

Modified to:

A subset of the primary small vessel vasculitides: Wegener's granulomatosis **(**also **commonly referred to** as granulomatosis with polyangiitis **[GPA])**, microscopic polyangiitis and Churg-Strauss syndrome (CSS), are characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) (Jennette and Falk, 1997).

Section 5.5.1 Prohibited Medications and Therapies that Result in Treatment Failure

Formerly:

- Corticosteroids for vasculitis:
  - doses > 20 mg/day prednisone (or equivalent) for > 1 week, or
  - IV corticosteroid pulses at any dose;
  Note: Doses of prednisone up to a maximum of 20 mg/day (or equivalent) for vasculitis, for a maximum of 1 week, are only allowable within the first 2 months of the double-blind treatment period.

Modified to:

- Corticosteroids for vasculitis:
  - doses > 20 mg/day prednisone (or equivalent), or
  - IV corticosteroid pulses at any dose;
  Note: Doses of prednisone up to a maximum of 20 mg/day (or equivalent) for vasculitis, for a maximum of 1 week, are only allowable within the first 2 months of the double-blind treatment period.

Section 5.5.3 Allowable Medications

Formerly:

The use of stable baseline dose regimens of corticosteroids (< 10 mg/day prednisone or equivalent) is permitted over the course of the trial. Doses of corticosteroid up to a maximum of 20 mg/day of prednisone (or equivalent), for vasculitis, are permitted for a maximum of

1 week within the first 2 months of the double-blind treatment period. At other times, subjects are restricted to ~~< 10 mg/day~~. Inhaled corticosteroids for asthma, or topical corticosteroids for atopic dermatitis are also permitted. Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or an IV corticosteroid pulse up to 125 mg prednisone (or equivalent) are permitted for reasons other than vasculitis (eg. acute allergic reaction), but a subject cannot receive more than 1 such corticosteroid regimen in any 365 day period (See also Section 5.5.1).

Modified to:

The use of stable baseline dose regimens of corticosteroids (**≤ 10** mg/day prednisone or equivalent) is permitted over the course of the trial. Doses of corticosteroid up to a maximum of 20 mg/day of prednisone (or equivalent), for vasculitis, are permitted for a maximum of 1 week within the first 2 months of the double-blind treatment period. At other times, subjects are restricted to **≤ 10** mg/day **prednisone or equivalent. It is expected that this dose may be tapered as clinically appropriate**. Inhaled corticosteroids for asthma, or topical corticosteroids for atopic dermatitis are also permitted. Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or an IV corticosteroid pulse up to 125 mg prednisone (or equivalent) are permitted for reasons other than vasculitis (eg. acute allergic reaction), but a subject cannot receive more than 1 such corticosteroid regimen in any 365 day period (See also Section 5.5.1).

Section 5.5.3.1 Azathioprine and Methotrexate

Formerly:

The target dose of azathioprine is 2 mg/kg/day (not to exceed 200 mg/day). Azathioprine ~~must be initiated at any time following confirmation of remission up to and including Day 0~~ at a dose of 50 mg/day and increased by no more than 50 mg/day every week until the target dose is achieved.

Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. These subjects will be included in the primary analysis.

~~It is recommended that~~ the appropriate local prescribing information (eg, contraindications, hematological and biochemical monitoring, pregnancy, contraception, etc.) for azathioprine or methotrexate (MTX) (as applicable), should be followed prior to and during treatment.

In the extension phase of the trial, the dose of AZA/MTX can be decreased or discontinued based on the discretion of the investigator.

Modified to:

The target dose of azathioprine is 2 mg/kg/day (not to exceed 200 mg/day). **For the maintenance of remission** azathioprine **may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine must not be initiated any later than Day 0. Azathioprine should be started** at a dose of 50 mg/day and increased by no more than 50 mg/day every week until the target dose is achieved.

Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. These subjects will be included in the primary analysis.

For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset. This should be discussed with the medical monitor. Methotrexate would not be recommended for those subjects with significantly impaired renal function.

*The appropriate local prescribing information (eg, **dose adjustments,** contraindications, hematological and biochemical monitoring, pregnancy, contraception, etc.) for azathioprine or methotrexate (MTX) (as applicable), should be followed prior to and during treatment.*

In the extension phase of the trial, the dose of AZA/MTX can be decreased or discontinued based on the discretion of the investigator.

Section 6.2 Study Enrollment Procedures

Formerly:

Subjects who have undergone all screening procedures and have met the entry criteria will be enrolled into the study and assigned to treatment by Interactive Web Response System (IWRS). Randomization will be performed on Day 0. ~~Day 0 (first administration of belimumab/placebo) must occur no more than 2 weeks after confirmation of remission. Azathioprine must be initiated at any time following confirmation of remission up to and including Day 0.~~ Female subjects who require pregnancy testing must have a negative urine pregnancy test done on Day 0, prior to randomization. Subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups (belimumab + AZA or placebo + AZA).

Modified to:

Subjects who have undergone all screening procedures and have met the entry criteria will be enrolled into the study and assigned to treatment by Interactive Web Response System (IWRS). Randomization will be performed on Day 0. **Azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine must not be initiated any later than Day 0.** Female subjects who require pregnancy testing must have a negative urine pregnancy test done on Day 0, prior to randomization. Subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups (belimumab + AZA or placebo + AZA).

Table 6-1 Study Calendar, Double-blind Treatment Phase Year One Footnotes

Formerly:

10. Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1mg/kg/day. If the patient continues to experience the toxicities described above a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted.

Modified to:

10. Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1mg/kg/day. If the patient continues to experience the toxicities described above a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. **For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset following discussion with the medical monitor.**

Section 7.1 Definitions

Formerly:

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. (ICH guidelines, March 1995)

Modified to:

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above **(eg, possible drug-induced liver injury)**. These should also usually be considered serious. (ICH guidelines, March 1995)

Section7.5 Progressive Multifocal Leukoencephalopathy

Formerly:

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

Modified to:

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. A diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The subject should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.

If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

Section 11 References

Added:

Jones,RB, Ferraro,AJ, Chaudhry,AN, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2009; 60: 2156-68.

Appendix 1 Chapel Hill Consensus Criteria for Wegener's Granulomatosis

Formerly:

Appendix 1 Chapel Hill Consensus ~~Criteria~~ for Granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) (Jennette et al, 2013)

The CHCC ~~Criteria~~ require:

Modified to:

Appendix 1 Chapel Hill Consensus **Definition** for Granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) (Jennette et al, 2013)

The CHCC **Definition** require**s**:

Appendix 2 Chapel Hill Consensus Criteria for Microscopic Polyangiitis

Formerly:

Appendix 2 Chapel Hill Consensus ~~Criteria~~ for Microscopic Polyangiitis (MPA) (Jennette et al, 2013)

The CHCC ~~criteria~~ require:

Modified to:

Appendix 2 Chapel Hill Consensus **Definition** for Microscopic Polyangiitis (MPA) (Jennette et al, 2013)

The CHCC **Definition** require**s**:

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Appendix 5 Vasculitis Damage Index

Added:

gsk GlaxoSmithKline | CONFIDENTIAL | | Final - 16 JUL 13
| **Protocol Identifier** | **BEL115466** |

VASCULITIS DAMAGE INDEX (VDI)
INVESTIGATOR INSTRUCTIONS

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

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gsk GlaxoSmithKline   CONFIDENTIAL   Final - 16 JUL 13

Protocol Identifier	Subject Identifier	Date of Assessment			Visit Description ✓ one:		
		Day	Month	Year	☐ Screening ☐ Day 0	☐ Year___ ☐ Week 12 ☐ Week 24 ☐ Week 36 ☐ Week 48 ☐ Exit	☐ OL Day 0 ☐ OL Week 24 ☐ OL Week 28/Exit
BEL115466							

VASCULITIS DAMAGE INDEX (VDI)

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

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, IV Belimumab

Added:

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in patients with SLE receiving immunosuppressant pharmacotherapy, including belimumab. Although the benefit-risk profile for belimumab remains unchanged following these events, the Sponsor considers that knowledge of these cases is important and has updated the clinical investigator's brochure (IB) for belimumab and revised the informed consent form (ICF) to communicate that development of PML is a potential risk.

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, Belimumab in ANCA-Associated Vasculitis, Study Overview and Patient Population

Formerly:

This is a Phase 3, multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen. Subjects enrolled into the study must have a clinical diagnosis of WG or MPA according to the Chapel Hill criteria and must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either CYC or RTX in the 6 months leading up to randomization. Subjects treated with 1 of the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- CYC 2 mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The ~~doses of CYC~~ are ~~given~~ as targets but may be adjusted for renal insufficiency or ~~white cell counts~~ as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ~~< 10~~ mg/day.

A target of 300 to 400 subjects ~~who are within~~ 26 weeks ~~of~~ starting induction therapy, achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving ~~less than~~ 10 mg/day prednisone (or equivalent) on 2 consecutive measurements ~~21 to 35~~ days apart will be enrolled into the study. Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter. Randomization will be performed on Day 0. ~~Day 0 (first administration of belimumab/placebo) must occur no more than 2 weeks after confirmation of remission.~~

All subjects (in both the belimumab and placebo groups) will be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. Azathioprine must be initiated ~~at any time following confirmation of remission up to and including Day 0. Patients with known intolerance to azathioprine will be excluded from the trial.~~ Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above, a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis.

Modified to:

This is a Phase 3, multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen. Subjects enrolled into the study must have a clinical diagnosis of WG or MPA according to the Chapel Hill criteria and must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either CYC or RTX in the 6 months leading up to randomization. Subjects treated with 1 of the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- **A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR**
- CYC 2 mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

[*The **cyclophosphamide dosing regimens** are **provided** as targets but may be adjusted for **older age, obesity,** renal insufficiency, **leukopenia,** or **other toxicities** as dictated by local practice.*]

For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by **0.5-**1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach **≤ 10** mg/day. **As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.**

A target of 300 to 400 subjects who are **between 6 and** 26 weeks **from** starting induction therapy, achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving **≤10** mg/day prednisone (or equivalent) on 2 consecutive measurements **at least 14** days apart will be enrolled into the study. Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter. Randomization will be performed on Day 0.

All subjects (in both the belimumab and placebo groups) will be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. **For the maintenance of remission, azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine must not be initiated any later than Day 0. For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset.** Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above, a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis.

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, Dose and Schedule, Induction and Maintenance Regimens for ANCA-Associated Vasculitis

Formerly:

Subjects participating in this trial will have had a moderate to severe episode of WG or MPA that was treated with high-dose corticosteroids (HDCS) and either RTX or CYC (IV or oral)

to induce the remission of the disease. Subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- CYC 2mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The ~~doses of~~ cyclophosphamide are ~~given~~ as targets but may be adjusted for renal insufficiency or ~~white cell counts~~ as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ~~<~~ 10 mg/day.

Rituximab was approved in April 2011 by the FDA for the treatment of WG and MPA. It has been used in induction of remission in AAV for a number of years, (Gorman et al, 2003, Smith et al, 2006) and 2 recent trials published in 2010 (Stone et al, 2010), demonstrated non-inferiority to induction with cyclophosphamide, the latter of these trials being used as the basis for the recent US approval. The RTX ~~regimen specified in this vasculitis study is the same~~ as that approved by the FDA for this indication.

Cyclophosphamide (2 mg/kg/day orally or IV 15 mg every 2 weeks for 3 doses and every 3 weeks thereafter) plus prednisone has been the standard induction regimen for WG and MPA since the early 1970s when initial work by Fauci and Wolff at the National Institutes of Health showed that this regimen induced disease remission in 12/14 patients and subsequent work showed that survival rates increased 80% using this regimen in what was previously an uniformly fatal disease (Fauci and Wolff, 1973; Fauci et al, 1983; Hoffman et al, 1992; Langford, 2011). Long term continued cyclophosphamide use, however, has been associated with significant toxicities (including infection, cystitis, cytopenias, and long term complications such as myelodysplasia and bladder cancer) and mortality (Langford, 2011).

A more recent study conducted by the European Vasculitis Group (Jayne et al, 2003) showed that after initial disease remission with cyclophosphamide and steroids, subjects could be switched to azathioprine (2 mg/kg/day) without having an increased risk of relapse compared to subjects whose remission was maintained using continued cyclophosphamide treatment. An induction regimen of CYC + prednisone followed by maintenance treatment with azathioprine is now considered the standard of care, given that administration of cyclophosphamide for longer durations does not offer an advantage from an efficacy standpoint and is associated with a greater potential for toxicity (Langford, 2011). The cyclophosphamide regimens described above are the same as those allowed in the inclusion criteria for this vasculitis study.

Once disease remission (defined as having, on 2 consecutive measurements ~~3 to 5~~ weeks apart: a BVAS v3 score of 0 and be receiving ~~< 10~~ mg/day of oral prednisone [or equivalent], ~~no more than~~ 26 weeks after the first dose of induction therapy) has been achieved, subject randomization into this protocol occurs. In this maintenance of remission trial, subjects will be randomized to receive a maintenance regimen of AZA (2 mg/kg/day) + placebo or AZA (2 mg/kg/day) + belimumab (10 mg/kg). Randomization in this protocol ~~must occur within 2 weeks of achieving a confirmed remission and the randomization~~ will be stratified by induction regimen.

The primary safety population for the SLE indication, including 473 subjects who were taking azathioprine as a concomitant medication at baseline, provides a substantial amount of safety data to support the conduct of the proposed trial. ~~In this study, subjects who have a known intolerance to azathioprine will be excluded.~~ Subjects naive to azathioprine and who experience azathioprine-related toxicity (Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT 2 times ULN, or a several gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting), following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience toxicities, a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis. The protocol instructs physicians to follow the appropriate local prescribing information for azathioprine or methotrexate (as applicable) prior to and during treatment.

Input on selection of these standard of care regimens was obtained from international experts in vasculitis, including members of the European Vasculitis Society (EUVAS) and the Vasculitis Clinical Research Consortium (VCRC), and consensus was reached that these regimens are appropriate for this international trial.

Complete details regarding the use of concurrent medications can be found in Section 5.5 of Protocol HGS1006-C1100.

Modified to:

Subjects participating in this trial will have had a moderate to severe episode of WG or MPA that was treated with high-dose corticosteroids (HDCS) and either RTX or CYC (IV or oral) to induce the remission of the disease. Subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- **A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR**
- CYC 2mg/kg/day orally plus HDCS OR

- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

*[The cyclophosphamide **dosing regimens** are **provided** as targets but may be adjusted for **older age, obesity,** renal insufficiency, **leukopenia,** or **other toxicities** as dictated by local practice.]*

For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 0.5-1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach **≤ 10** mg/day. **As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.**

Rituximab was approved in April 2011 by the FDA for the treatment of WG and MPA. It has been used in induction of remission in AAV for a number of years, (Gorman et al, 2003, Smith et al, 2006) and 2 recent trials published in 2010 (Stone et al, 2010), demonstrated non-inferiority to induction with cyclophosphamide, the latter of these trials being used as the basis for the recent US approval. The RTX **dosing regimen of 4 infusions of 375 mg/m^2 each given 1 week apart reflects the dosing regimen** that **is** approved by the FDA for this indication. **An alternative RTX induction regimen (2 infusions of 1 gram each administered 2 weeks apart) is also offered in the protocol. Although the latter regimen is not licensed as an induction therapy for ANCA-vasculitis, it is very widely used in clinical practice and clinical evidence suggests that there is no difference between the two dosing regimens in terms of duration of B-cell depletion or therapeutic efficacy efficacy (Jones et al, 2009).**

Cyclophosphamide (2 mg/kg/day orally or IV 15 mg every 2 weeks for 3 doses and every 3 weeks thereafter) plus prednisone has been the standard induction regimen for WG and MPA since the early 1970s when initial work by Fauci and Wolff at the National Institutes of Health showed that this regimen induced disease remission in 12/14 patients and subsequent work showed that survival rates increased 80% using this regimen in what was previously an uniformly fatal disease (Fauci and Wolff, 1973; Fauci et al, 1983; Hoffman et al, 1992; Langford, 2011). Long term continued cyclophosphamide use, however, has been associated with significant toxicities (including infection, cystitis, cytopenias, and long term complications such as myelodysplasia and bladder cancer) and mortality (Langford, 2011).

A more recent study conducted by the European Vasculitis Group (Jayne et al, 2003) showed that after initial disease remission with cyclophosphamide and steroids, subjects could be switched to azathioprine (2 mg/kg/day) without having an increased risk of relapse compared to subjects whose remission was maintained using continued cyclophosphamide treatment. An induction regimen of CYC + prednisone followed by maintenance treatment with azathioprine is now considered the standard of care, given that administration of cyclophosphamide for longer durations does not offer an advantage from an efficacy standpoint and is associated

with a greater potential for toxicity (Langford, 2011). The cyclophosphamide regimens described above are the same as those allowed in the inclusion criteria for this vasculitis study.

Once disease remission (defined as having, on 2 consecutive measurements **at least 14 days** apart: a BVAS v3 score of 0 and be receiving ≤ **10** mg/day of oral prednisone [or equivalent], **between 6 and** 26 weeks after the first dose of induction therapy) has been achieved, subject randomization into this protocol occurs. In this maintenance of remission trial, subjects will be randomized to receive a maintenance regimen of AZA (2 mg/kg/day) + placebo or AZA (2 mg/kg/day) + belimumab (10 mg/kg). Randomization in this protocol will be stratified by induction regimen.

The primary safety population for the SLE indication, including 473 subjects who were taking azathioprine as a concomitant medication at baseline, provides a substantial amount of safety data to support the conduct of the proposed trial. **For the maintenance of remission, azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy and no later than Day 0. For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset.** Subjects naive to azathioprine and who experience azathioprine-related toxicity (Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT 2 times ULN, or a several gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting), following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience toxicities, a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis. The protocol instructs physicians to follow the appropriate local prescribing information for azathioprine or methotrexate (as applicable) prior to and during treatment.

Input on selection of these standard of care regimens was obtained from international experts in vasculitis, including members of the European Vasculitis Society (EUVAS) and the Vasculitis Clinical Research Consortium (VCRC), and consensus was reached that these regimens are appropriate for this international trial.

Complete details regarding the use of concurrent medications can be found in Section 5.5 of Protocol HGS1006-C1100.

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, Safety Considerations

Added:

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

immunosuppressant pharmacotherapy, including belimumab. Therefore, a diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The protocol requires that subjects should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy. If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

Protocol Amendment 02, 25 April 2013
Protocol Number: HGS1006-C1100

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The protocol has been modified to include testing at Screening for HIV antibody, to expand Hepatitis B serology testing, and to exclude patients who test positive according to the criteria specified.
2. Because the RIBA antibody confirmation assay for hepatitis C is not available due to non-availability of manufacturer's reagents, an alternative test, HCV RNA-PCR assay, will be used to detect the presence of viral RNA, and hence confirm a current infection.
3. The protocol has been modified to exclude patients at baseline with abnormal liver function according to the criteria specified.
4. A new section has been added to clarify how patient care should be managed if a patient has a liver chemistry event during the study. The accompanying figure has been placed in an appendix (Appendix 13) and the List of Appendices has been updated accordingly.
5. Measurement of vital signs (temperature, sitting blood pressure [systolic and diastolic], and heart rate) have been added to the procedures for all scheduled study visits and a 12-lead ECG has been added to the procedures for the Day 0 visit. These procedures have been added to provide increased understanding and to assist analyses of potential safety events should they occur.
6. A page with the protocol's revision chronology has been added.
7. The Synopsis has been corrected to include study agent dosing on day 28.
8. Text has been added to clarify that study agents (belimumab or placebo) will be provided by the sponsor during the double-blind treatment phase and that belimumab will be provided by the sponsor during the open-label extension phase.
9. Within the definition of postmenopausal in Inclusion Criterion #7, "1 year without menses" has been changed to "12 consecutive months with no menses without an alternative medical cause." Also, the sub-bullet formatting of the last 8 rows of Inclusion Criterion #7 has been corrected.
10. Steroid use for vasculitis has been modified to restrict the use of corticosteroids up to a maximum of 20 mg/day of prednisone (or equivalent) for a maximum of 1 week within the first 2 months of the double-blind treatment period, and at other times, to < 10 mg/day.
11. The Reference List has been updated to include references cited in text but not present in the list and to delete a reference included in error. Also, the in text citation for Posner et al has been corrected to Posner et al 2007 and the reference has been added to the list.
12. Cross-references have been added in Section 1 for references that were in the Reference List but which inadvertently had not been cited in text.

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13. In Appendix 8, for the question at baseline/screening "Is the time the subject felt most suicidal (i.e. the lifetime rating) more than X month(s) ago?", the "X" has been corrected to "2", i.e, "more than 2 month(s) ago".

14. The investigator evaluation of adverse events regarding causality has been modified from a multi-choice assessment (definitely related, probably related, etc.) to an assessment of "reasonable possibility".

15. Appendix 9 has been corrected to cite the reference and the publication has been added to the Reference List.

16. Two new appendices have been added to provide the questionnaires for the PSRHQ (Appendix 10) and the PSRQ (Appendix 11) and cross-references added in-text as appropriate. The List of Appendices has been updated accordingly.

17. The protocol has been modified to include a Benefit and Risk Assessment (Appendix 12). The List of Appendices has been updated accordingly.

18. Minor administrative change was made for presentation of cross-referencing sections and tables, e.g., "see Sections X.1 and X.2" was changed to "see Section X.1 and Section X.2". These minor changes are not shown in the Modifications section below.

19. The list of abbreviations has been updated to add abbreviations as a result of new and/or amended text and to correct previous errors.

20. The Chapel Hill Consensus Conference (CHCC) definitions for Wegener's granulomatosis and microscopic polyangiitis in Appendices 1 and 2 of the protocol have been updated to reflect the most recent CHCC (2012) definitions. The reference for this (Jeannette et al 2013) is cited in the text (Section 1.1) and in the reference list.

Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment: 01
Date: 22 June 2012

Modified to:

Protocol Amendment **02**
Date: **25 April** 201**3**

Revision Chronology for HGS1006-C1100 (BEL115466)

Added:

	Date	Document*
Global	07 March 2012	Original
Global	22 June 2012	Amendment No 01
Local	29 January 2013	Addendum 01 for Sweden
Local DNG2013N160488_01	31 January 2013	Addendum 01 for Ireland
Global DNG2013N167980_00	25 April 2013	Amendment No 02

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

Synopsis, Diagnosis & Inclusion Criteria
Section 4.1, Inclusion Criteria

Formerly:

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

Modified to:

7. A female subject is eligible to enter the study if she is:
   - Not pregnant or nursing;
   - Of non-childbearing potential (ie, women who had a hysterectomy, are postmenopausal which is defined as **12 consecutive months with no menses without an alternative medical cause**, have both ovaries surgically removed or have current documented tubal ligation or other permanent sterilization procedure); <u>or</u>
   - Of childbearing potential (ie, women with functional ovaries and no documented impairment of oviductal or uterine function that would cause sterility). This category includes women with oligomenorrhoea [even severe], women who are peri-menopausal or have just begun to menstruate. These women must have a negative serum pregnancy test at screening, and agree to 1 of the following:
     o Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent; <u>or</u>
     o Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:
       o Implants of levonorgestrel or etonogestrel;
       o Injectable progesterone;
       o Transdermal contraceptive patch
       o Any intrauterine device (IUD) with a documented failure rate of less than 1% per year;
       o Oral contraceptives (either combined or progesterone only);
       o Ethinyl estradiol/Etonogestrel vaginal ring
       o Double barrier method: Condom and Occlusive cap (diaphragm or cervical/vault caps) with spermidical foam/gel/film/cream/suppository; or
       o 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.

Synopsis, Exclusion Criteria and Section 4.2, Exclusion Criteria

Formerly:

12. Have a historically positive test or test positive at screening for hepatitis B surface antigen, or hepatitis C antibody or are known to be HIV-1 positive.

Modified to:

12. Have a historically positive HIV test or test positive at screening for HIV.

13. Hepatitis B: Serologic evidence of Hepatitis B (HB) infection based on the results of testing for HBsAg, anti-HBc and anti-HBs as follows:

- **Patients positive for HBsAg are excluded.**
- **Patients negative for HBsAg and anti-HBc antibody but positive for anti-HBs antibody and with no history of Hepatitis B vaccination are excluded.**
- **Patients negative for HBsAg but positive for both anti-HBc and anti-HBs antibodies are excluded.**
- **Patients negative for HBsAg and anti-HBs antibody but positive for anti-HBc antibody are excluded.**

14. Hepatitis C: Positive test for Hepatitis C antibody confirmed on a subsequent blood sample by RNA-PCR assay. Subjects who are positive for Hepatitis C antibody and negative when the Hepatitis C RNA-PCR assay is performed on a subsequent sample will be eligible to participate. Subjects who are positive for Hepatitis C antibody and have a positive result for the HCV when the Hepatitis C RNA-PCR assay is performed on the subsequent sample will not be eligible to participate.

Added:

19. Subjects who have abnormal liver function tests defined as follows: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\geq$ 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%).

Synopsis, Section Study Design and Schedule

Formerly:

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter.

Modified to:

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). **Belimumab or placebo will be supplied by the sponsor during this double-blind treatment phase.** It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, **28,** and every 28 days thereafter.

Formerly:

If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months.

Modified to:

If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months **and this will be supplied by the sponsor**.

Section List of Abbreviations

Formerly:

| ALT | aspartate aminotransferase alanine |
| LDH | lactic dehydrogenase |

Modified to:

| ALT | **alanine** aminotransferase |
| LDH | **lactate** dehydrogenase |

Added:

CPK	**creatine phosphokinase**
ECG	**electrocardiogram**
HB	**hepatitis B**
HBsAg	**hepatitis B surface antigen**
HBc	**hepatitis B core**
HCV	**hepatitis C virus**

Section 1.1 Disease Background

Formerly:

Anti-PR3 antibodies are associated with increased morbidity and mortality compared to anti-MPO. The most widely used classification criteria for diagnosing the 3 types of AAV are those published by the American College of Rheumatology (ACR) for WG and CSS (Leavitt et al, 1990 and Masi et al, 1990, respectively), and that published by the Chapel Hill Consensus Conference (CHCC) for MPA (Jennette et al, 1994).

The precise epidemiology of these diseases is uncertain as early studies did not utilize the same classification criteria as later ones (Koldingsnes and Nossent, 2008; Watts et al, 2007).

In the US, the prevalence rates of WG range from 2.6-9/100000 (Mahr et al, 2006).

Modified to:

Anti-PR3 antibodies are associated with increased morbidity and mortality compared to anti-MPO **(Hogan et al, 1996; Franssen et al, 1998)**. The most widely used classification criteria for diagnosing the 3 types of AAV are those published by the American College of Rheumatology (ACR) for WG and CSS (Leavitt et al, 1990 and Masi et al, 1990, respectively), and that published by the Chapel Hill Consensus Conference (CHCC) for MPA (Jennette et al, 1994; **Jennette et al, 2013**).

The precise epidemiology of these diseases is uncertain as early studies did not utilize the same classification criteria as later ones (Koldingsnes and Nossent, 2008; Watts et al, 2007; **Mahr, 2009**).

In the US, the prevalence rates of WG range from 2.6 9/100000 (**Zeft et al, 2005;** Mahr et al, 2006).

Section 1.3.1 Belimumab Administered Intravenously

Added:

A benefit-risk evaluation of belimumab in the context of the present study is provided in Appendix 12 of this protocol.

Section 1.4 Rationale for the Study

Formerly:

The fact that rituximab, a biologic therapy that targets B cells by binding to the B cell surface antigen CD20, recently showed success in inducing remission in AAV (Stone et al, 2010) and was granted approval for the treatment of WG and MPA supports the rationale that belimumab, which down regulates B cells by targeting BLyS, may be useful in the treatment of this disease.

Modified to:

The fact that rituximab, a biologic therapy that targets B cells by binding to the B cell surface antigen CD20 **(Dass et al, 2008; Wang et al 2008)**, recently showed success in inducing remission in AAV (Stone et al, 2010) and was granted approval for the treatment of WG and MPA supports the rationale that belimumab, which down regulates B cells by targeting BLyS, may be useful in the treatment of this disease.

Section 3.1 Basic Design Characteristics

Formerly:

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter.

Modified to:

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). **Belimumab or placebo will be supplied by the sponsor during this double-blind treatment phase.** It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, 28, and every 28 days thereafter.

Formerly:

If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given

the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months.

Modified to:

If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months **and this will be supplied by the sponsor**.

Section 5.5.1 Prohibited Medications and Therapies that Result in Treatment Failure

Formerly:

- Corticosteroids for vasculitis:
  - doses > 20 mg/day prednisone (or equivalent), or
  - IV corticosteroid pulses at any dose;

Modified to:

- Corticosteroids for vasculitis:
  - doses > 20 mg/day prednisone (or equivalent) **for > 1 week**, or
  - IV corticosteroid pulses at any dose;
  Note: Doses of prednisone up to a maximum of 20 mg/day (or equivalent) for vasculitis, for a maximum of 1 week, are only allowable within the first 2 months of the double-blind treatment period.

Section 5.5.3 Allowable Medications

Formerly:

The use of stable baseline dose regimens of corticosteroids (< 10 mg/day prednisone or equivalent) is permitted over the course of the trial. Inhaled corticosteroids for asthma, or topical corticosteroids for atopic dermatitis are also permitted. Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or an IV corticosteroid pulse up to 125 mg prednisone (or equivalent) are permitted for reasons other than vasculitis (eg. acute allergic reaction), but a subject cannot receive more than 1 such corticosteroid regimen in any 365 day period (See also Section 5.5.1).

Modified to:

The use of stable baseline dose regimens of corticosteroids (< 10 mg/day prednisone or equivalent) is permitted over the course of the trial. **Doses of corticosteroid up to a maximum of 20 mg/day of prednisone (or equivalent), for vasculitis, are permitted for a maximum of 1 week within the first 2 months of the double-blind treatment period. At other times, subjects are restricted to < 10 mg/day.** Inhaled corticosteroids for asthma, or topical corticosteroids for atopic dermatitis are also permitted. Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or an IV corticosteroid pulse up to 125 mg prednisone (or equivalent) are permitted for reasons other than vasculitis (eg. acute allergic reaction), but a subject cannot receive more than 1 such corticosteroid regimen in any 365 day period (See also Section 5.5.1).

Section 6.1 Screening Procedures (Day -60 to Day 0):

Formerly:

- Blood samples for: (see Appendix 6 – Laboratory Tests)
  - Hepatitis B surface antigen, and Hepatitis C antibody testing

Modified to:

- Blood samples for: (see Appendix 6 – Laboratory Tests)
  - **HIV antibody testing, serologic investigations for Hepatitis B (HB) infection (**HBsAg, **anti-HBc, and anti-HBs), and** Hepatitis C antibody testing ± **confirmatory HCV RNA-PCR testing**

Table 6-1 Study Calendar, Double-blind Treatment Phase Year One
Vital signs: All scheduled visits

Formerly:

Not listed.

Modified to:

Vital signs[15, 16] is added to the study calendar under Clinical Assessments.

Vital signs is marked "**X**" as required at all scheduled visits.

Table 6-1 Study Calendar, Double-blind Treatment Phase Year One
12-lead ECG: Day 0 Visit

Formerly:

Not listed.

Modified to:

12-lead ECG[16] is added to the study calendar under Clinical Assessments.

12-lead ECG is marked "**X**" as required at this visit.

Table 6-1 Study Calendar, Double-blind Treatment Phase Year One
HIV, Hepatitis B, C: Screening Visits

Formerly:

Hep B surface antigen & Hep C antibody

Modified to:

HIV, Hepatitis B, C[17]

HIV, Hepatitis B, C is marked "**X**" as required at this visit.

Table 6-1 Study Calendar, Double-blind Treatment Phase Year One
Footnotes

Formerly:

[1]Complete physical examination, including height, weight and vital signs.

Modified to:

[1]Complete physical examination, including height and weight.

A*dded:*

[15]Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate.

[16]Complete prior to dosing.

[17]HIV, Hepatitis B surface antigen, anti-HBc, anti-HBs and hepatitis C antibody (if hepatitis C antibody positive, HCV RNA-PCR assay will be performed on a subsequent blood sample to confirm the results).

**Table 6-2 Study Calendar, Double-blind Treatment Phase Additional Years
Vital signs: All scheduled visits**

Formerly:

Not listed.

Modified to:

Vital signs[11, 12] is added to the study calendar under Clinical Assessments.

Vital signs is marked "**X**" as required at all scheduled visits.

**Table 6-2 Study Calendar, Double-blind Treatment Phase Additional Years
Footnotes**

Added

[11]Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate.

[12]Complete prior to dosing.

**Table 6-3 Study Calendar, Open-Label Extension Phase
Vital signs: All scheduled visits**

Formerly:

Not listed.

Modified to:

Vital signs[11, 12] is added to the study calendar under Clinical Assessments.

Vital signs is marked "**X**" as required at all scheduled visits.

**Table 6-3 Study Calendar, Open-Label Extension Phase
Footnotes**

Added:

[11]Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate.

[12]Complete prior to dosing.

Section 6.6 Laboratory Tests

The following section has been added:

Section 6.6.2 Phase III-IV Liver Chemistry Stopping and Follow-up Criteria

The liver chemistry stopping and follow-up criteria have been designed to assure subject safety and evaluate liver event etiology.

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

1. ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥ 3xULN and INR>1.5, if INR measured).
    NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug from that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. ALT ≥ 8xULN.
3. ALT ≥ 5xULN but <8 xULN persists for ≥2 weeks.
4. ALT ≥ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice), or hypersensitivity (such as fever, rash or eosinophilia).
5. ALT ≥ 5xULN but <8 xULN and cannot be monitored weekly for ≥2 weeks.

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

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

    NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug from that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

*   Complete the liver imaging and/or liver biopsy CRFs if these tests are performed

- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.

- Withdraw the subject from the **study** (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
- Do not re-start investigational product.

In addition, for criterion 1:

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

For criteria 2, 3, 4 and 5:

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

Subjects with ALT ≥5xULN and <8xULN which exhibit a decrease to ALT ≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety
- Can continue investigational product
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

For criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- • Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);

- Hepatitis C RNA;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Hepatitis E IgM antibody;
- Blood sample for PK analysis, obtained within approximately 1 to 2 weeks after the liver event. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Procedures Manual.
- 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, paracetamol (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 and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

Section 7.6 Suicidality Assessment

Formerly:

Subjects who answer "yes" to any suicidal behavior or "yes" to suicidal ideation questions 4 or 5 on the C-SSRS should be referred to appropriate psychiatric care and prompts the completion of an SAE worksheet. The medical monitor should be notified when these events occur. In addition, a "yes" to any suicidal behavior or "yes" to suicidal ideation question 3, 4 or 5 on the C-SSRS prompts the completion of the Possible Suicidality Related History

Questionnaire (PSRHQ, only the first time this condition is met) eCRF and a Possible Suicidality Related Questionnaire (PSRQ) eCRF (at all times this condition is met).

Baseline/Screening and during treatment assessment of suicidality will be performed during the blinded portion of this study using C-SSRS (Refer to Appendix 8 for C-SSRS). The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both behaviour and ideation (Posner et al, 2010).

Modified to:

Subjects who answer "yes" to any suicidal behavior or "yes" to suicidal ideation questions 4 or 5 on the C-SSRS should be referred to appropriate psychiatric care and prompts the completion of an SAE worksheet. The medical monitor should be notified when these events occur. In addition, a "yes" to any suicidal behavior or "yes" to suicidal ideation question 3, 4 or 5 on the C-SSRS prompts the completion of the Possible Suicidality Related History Questionnaire (PSRHQ, only the first time this condition is met**; refer to Appendix 10 for the PSRHQ**) eCRF and a Possible Suicidality Related Questionnaire (PSRQ) eCRF (at all times this condition is met**; refer to Appendix 11 for the PSRQ**).

Baseline/Screening and during treatment assessment of suicidality will be performed during the blinded portion of this study using C-SSRS (Refer to Appendix 8 for C-SSRS). The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both behaviour and ideation (Posner et al, **2007**).

Section7.6.1 Possible Suicidality Related Questionnaire (PSRQ)

Formerly:

The investigator will be prompted to complete the PSRQ (in addition to the AE or SAE pages, as appropriate) if a yes response is given to any suicidal behavior or a yes response to suicidal ideation questions 3, 4 or 5 on the C-SSRS.

Modified to:

The investigator will be prompted to complete the PSRQ (in addition to the AE or SAE pages, as appropriate) if a yes response is given to any suicidal behavior or a yes response to suicidal ideation questions 3, 4 or 5 on the C-SSRS. **Refer to Appendix 11 for the PSRQ.**

Section 7.8 Investigator Evaluation of Adverse Events

Formerly:

CAUSALITY

Definitely Related   - reasonable temporal relationship to study agent administration

                        - follows a known response pattern (eg, study agent is known to cause
                          this AE)
                        - there is no alternative etiology

Probably Related   - reasonable temporal relationship
                        - follows a suspected response pattern (eg, based on similar drugs)
                        - no evidence for a more likely alternative etiology

Possibly Related   - reasonable temporal relationship
                        - little evidence for a more likely alternative etiology

Probably Not Related   - does not have a reasonable temporal relationship OR
                        - good evidence for a more likely alternative etiology

Not Related   - does not have a temporal relationship OR
                        - definitely due to alternative etiology

The causality assessment must be made by the investigator based on information available at the time that the AE eCRF or SAE worksheet is completed. The initial causality assessment may be revised as new information becomes available.

Modified to:

CAUSALITY

It is a regulatory requirement for investigators to assess relationship between the investigational product(s) and the occurrence of each AE/SAE based on the information available. The assessment should be reviewed on receipt of any new information and amended if necessary. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support "a reasonable possibility" include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

Section 11 References

Formerly:

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Modified to:

Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009; 68:1827-32. **doi: 10.1136/ard.2008.101279. Epub 2008 Dec3**.

Added:

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Deleted:

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Appendix 1 Chapel Hill Consensus Criteria for Wegener's Granulomatosis

Formerly:

The CHCC Criteria require:

Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (eg, capillaries, venules, arterioles, and arteries) for a diagnosis of Wegener's.

Another symptoms that may be present in WG, but that are not required according the CHCC classification scheme, is necrotizing glomerulonephritis.

Modified to:

Appendix 1 Chapel Hill Consensus Criteria for **Granulomatosis with polyangiitis (GPA) (**Wegener's Granulomatosis**) (Jennette et al, 2013)**

The CHCC Criteria require:

Necrotizing granulomatous inflammation **usually** involving the **upper and lower** respiratory tract, and necrotizing vasculitis affecting **predominantly** small to medium-sized vessels (eg, capillaries, venules, arterioles, and arteries) for a diagnosis of Wegener's.

Another feature that may be **commonly** present in **GPA**, but **which is** not required according **to** the CHCC **definition**, is necrotizing glomerulonephritis.

Appendix 2 Chapel Hill Consensus Criteria for Microscopic Polyangiitis

Formerly:

The CHCC criteria require:

Necrotizing vasculitis with few or no immune deposits that affects small vessels (ie, capillaries, venules, or arterioles) for a diagnosis of MPA.

Other symptoms that may be present in MPA, but that are not required according the CHCC classification scheme, are: necrotizing arteritis involving small- and medium-sized vessels; glomerulonephritis; and pulmonary capilliaritis.

Modified to:

Appendix 2 Chapel Hill Consensus Criteria for Microscopic Polyangiitis **(MPA) (Jennette et al, 2013)**

The CHCC criteria require:

Necrotizing vasculitis, with few or no immune deposits, **predominantly affecting** small vessels (ie, capillaries, venules, or arterioles) for a diagnosis of MPA. **Granulomatous inflammation is absent.**

Other **features** that may be present in MPA, but that are not required according **to** the CHCC **definition**, are: necrotizing arteritis involving small- and medium-sized arteries; **commonly necrotizing** glomerulonephritis; and **often** pulmonary **capillaritis**.

Appendix 6 Laboratory Tests

Formerly:

Enzymes:
    SGOT (AST)
    SGPT (ALT)
    Alkaline Phosphatase
    Gamma glutamyl transferase (GGT)
    Lactic dehydrogenase (LDH)
Other:
    Creatinine
    Blood urea nitrogen (BUN)
    BUN/creatinine ratio
    Bilirubin, total
    Protein, total
    Albumin
    Uric acid
    Glucose
    Hepatitis C antibody
    Hepatitis B surface antigen
    Estimated Creatinine Clearance/ GFR (Cockcroft-Gault)

Modified to:

Enzymes:
    SGOT (AST)
    SGPT (ALT)
    Alkaline Phosphatase
    Gamma glutamyl transferase (GGT)
    Lactate dehydrogenase (LDH)
Other:
    Creatinine
    Blood urea nitrogen (BUN)
    BUN/creatinine ratio
    Bilirubin, total
    Protein, total
    Albumin
    Uric acid

Glucose

HIV-1/2 antibody

Hepatitis C **antibody (± HCV RNA PCR for confirmation of positive antibody test)**

Hepatitis B surface antigen

Hepatitis B surface and core antigen antibodies

Estimated Creatinine Clearance/ GFR (Cockcroft-Gault)

Liver event follow-up assessments:

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

Footnote added:

Appendix 6 Laboratory Tests[1]

[1]   **Institution or country specific guidelines for blood sample volume limits must be followed in collection of the subsequent blood sample.**

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

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

Modified to:

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

Appendix 9 Pharmacogenetic Research, Research Rationale

Formerly:

Systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies but little is known regarding the genetic contribution to risk for developing different forms of vasculitis. Recent gene studies in vasculitis are identifying both common polymorphisms associated with other autoimmune but also completely different associations.

There is growing evidence for a genetic contribution to the risk of developing different forms of vasculitis (Monach, 2010) for example the association of alpha 1-antitrypsin deficiency in WG.

Modified to:

Systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies but little is known regarding the genetic contribution to risk for developing different forms of vasculitis. Recent gene studies in vasculitis are identifying both common polymorphisms associated with other autoimmune but also completely different associations **(Monach and Merkel, 2010)**.

There is growing evidence for a genetic contribution to the risk of developing different forms of vasculitis (Monach **and Merkel,** 2010) for example the association of alpha 1-antitrypsin deficiency in WG.

Appendix 10 Possible Suicidality Related History Questionnaire (PSRHQ)

Added:

	CONFIDENTIAL	
gsk GlaxoSmithKline	**Protocol Identifier** | **BEL115466**	Final - 16 JAN 13

POSSIBLE SUICIDALITY-RELATED HISTORY QUESTIONNAIRE (PSRHQ) INSTRUCTIONS

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

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

And/or

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

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

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

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

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gsk GlaxoSmithKline   CONFIDENTIAL   Final - 16 JAN 13

Protocol Identifier	Subject Identifier		Visit Description
BEL115466		WORKSHEET	

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

POSSIBLE SUICIDALITY-RELATED HISTORY QUESTIONNAIRE

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

[Y] ☐ Yes [N] ☐ No

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

	Event	Date (DDMMMYYYY)
☐	Cerebrovascular Accident	
☐	Headache	
☐	Meningitis	
☐	Organic Confusion	
☐	Seizures	

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

Appendix 11 Possible Suicidality Related Questionnaire (PSRQ)

Added:

	CONFIDENTIAL	
gsk GlaxoSmithKline	**Protocol Identifier**	**BEL115466**

Final - 15 JAN 13

POSSIBLE SUICIDALITY-RELATED QUESTIONNAIRE (PSRQ) INSTRUCTIONS

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

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

And/or

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

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

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

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

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

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

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

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

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

gsk GlaxoSmithKline   CONFIDENTIAL   Final - 15 JAN 13

Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
BEL115466			_____

Date of assessment [ ][ ] [ ][ ] [ ][ ][ ][ ]
                   Day   Month   Year

POSSIBLE SUICIDALITY-RELATED QUESTIONNAIRE (PSRQ)

☐ **Not Done**

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

If Yes, check all that apply:

☐ Amphetamines   ☐ Benzodiazepines   ☐ Cannabinoids   ☐ Cocaine   ☐ Opiates

☐ Other, Specify: _____

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

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

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

If Yes, check all that apply:

☐ Family Problems   ☐ Relationships   ☐ Employment/ Unemployment   ☐ Finances

☐ Other Factors, Specify:_____

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

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

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

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

If Yes, specify disorder next to all that apply:

Father   _____

Mother   _____

Sibling   _____

Other   _____

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

Appendix 12 Protocol Addendum – Benefit and Risk Assessment

Added:

Disease Background

The systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies including infective and drug-induced causes and can be either primary or secondary to other diseases such as SLE. A subset of the primary small vessel vasculitides: Wegener's granulomatosis; also known as granulomatosis with polyangiitis (GPA), microscopic polyangiitis and Churg-Strauss syndrome (CSS), are characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) (Jennette and Falk, 1997). ANCA-associated vasculitides (AAV) are multisystem diseases with a broad range of manifestations from cutaneous ulcers, scleritis, pericarditis to lifethreatening manifestations such as lung hemorrhage and renal failure. All 3 forms of AAV share the characteristic of systemic necrotizing vasculitis; WG and CSS are further characterized by granuloma formation.

Historically, ANCA have been classified on the basis of their staining patterns in immunofluoresence assays as either cytoplasmic (C-ANCA) or perinuclear (P-ANCA). It is now recognized that in AAV, C-ANCA is usually directed against proteinase 3 (PR3), and P-ANCA is generally directed against myeloperoxidase (MPO), both of which are enzymes that are abundant in the granules of neutrophils (Jennette and Falk, 1997; Merkel et al, 1997). Anti-PR3 antibodies are generally associated with WG, while anti-MPO autoantibodies are more common in MPA and CSS. Anti-PR3 antibodies are associated with increased morbidity and mortality compared to anti-MPO. The most widely used classification criteria for diagnosing the 3 types of AAV are those published by the American College of Rheumatology (ACR) for WG and CSS (Leavitt et al, 1990 and Masi et al, 1990, respectively), and that published by the Chapel Hill Consensus Conference (CHCC) for MPA (Jennette et al, 1994). Of note, none of these diagnostic criteria incorporate the measurement of ANCA.

The precise epidemiology of these diseases is uncertain as early studies did not utilize the same classification criteria as later ones (Koldingsnes and Nossent, 2008; Watts et al, 2007). In the case of MPA, in particular, epidemiological studies are confounded by its original inclusion as a form of polyarteritis nodosa (PAN). Utilizing the ACR or CHCC criteria, prevalence rates range from 5-16/100000 for WG, 2.5-9.4/100000 for MPA, and 0.4-1.4/100000 for CSS making the latter the least prevalent of the three by some margin (Koldingsnes et al, 2008). AAV are extremely rare in childhood with peak age of onset in those aged 65 to 74 years (Ntatski et al, 2010), with other small vessel vasculitides being the major concern in childhood (Brogan et al, 2010).Current therapy is usually determined by severity of the disease, with more severe forms warranting more aggressive approaches. These usually involve an initial remission induction regimen of high dose corticosteroid administered with either cyclophosphamide (CYC) or rituximab (RTX) followed by a remission maintenance period usually with azathioprine (Stone et al, 2010; Bosch et al, 2007; Jayne et al, 2003). Minor manifestations are usually treated with low dose corticosteroid

administered with either azathioprine or methotrexate (Belmont, 2006). Even with recent treatment advances the morbidity and mortality of patients with AAV remains unacceptably high (Drooger et al, 2009).

The Birmingham Vasculitis Activity Score (BVAS) was developed and validated as a tool to measure disease activity (Luqmani et al, 1994). It has been modified to form the BVAS/WG (Stone et al, 2001) and updated most recently with the validation of version 3 of the instrument, also known as BVAS 2003 (Mukhtyar et al, 2009). In its current form it is a list of 56 items which are considered to be manifestations of vasculitis. A weighted numerical score is attached to each item to reflect the importance of each manifestation. The items are grouped by organ systems, and each organ system has a maximum or 'ceiling' score to reflect the relative importance of the organ system (Mukhtyar et al, 2009). The tool also makes a distinction between new or worsening disease and persistent disease with new or worsening attracting higher scores.

IV Belimumab

Over 2,000 individuals with SLE have been treated with belimumab in clinical studies. In two global Phase 3 studies, belimumab 10 mg/kg met the primary efficacy endpoint (SRI at Week 52). Evidence of other possible benefits in these trials included reductions in risk of severe flare and corticosteroid use, and improvements in patient reported quality of life and fatigue. Serological activity was reduced as measured by reductions in autoantibodies and normalization of hypergammaglobulinemia and complement levels. B cells, including autoreactive B cells, were also reduced, but not severely depleted, consistent with what would be expected from inhibition of BLyS (reference belimumab IB, Section 5.3.1). These results supported the approval of belimumab in the EU, US, Canada and other countries.

In the United States belimumab is approved for the following indication:

BENLYSTA® (belimumab) is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

Limitations of Use: The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of BENLYSTA is not recommended in these situations.

In the EU, the approved indication focuses on patients with high disease activity (where belimumab offered the greatest benefit):

Benlysta is indicated as add-on therapy in adult patients with active, autoantibodypositive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g positive anti-dsDNA and low complement) despite standard therapy.

The EU SPC also includes special warnings and precautions for use similar to the US labeling, including that belimumab has not been studied in and is thus not recommended in

patients with severe active central nervous system lupus or severe active lupus nephritis. In addition, caution should be exercised if belimumab is co-administered with other B cell targeted therapy or cyclophosphamide. Reference Section 4.4 of the SPC for the complete list of specials warnings and precautions.

Treatment with belimumab plus standard therapy was generally well tolerated, with rates of AEs, severe AEs, SAEs, AEs leading to discontinuation, and serious/severe infections generally comparable to the rates observed in the placebo plus standard therapy group. The most commonly-reported adverse reactions, occurring in $\geq 3\%$ of patients receiving 10 mg/kg belimumab IV in clinical trials (and at a $\geq 1\%$ greater rate than placebo) were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, cystitis, leukopenia, and gastroenteritis viral. In clinical trials, hypersensitivity and infusion reactions were observed more frequently with belimumab, with anaphylaxis observed in $\leq 1\%$ of subjects. Data from the post-marketing setting indicate that hypersensitivity reactions may be serious or result in death, that the onset of such reactions may be delayed, and that patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. In addition, it is also known from clinical trials and the post-marketing setting that the vast majority of hypersensitivity reactions occur with the 1st or 2nd infusion. The product labeling, belimumab IB, protocol, and informed consent forms have been updated to include this new information, as applicable.

Other risks that may be associated with belimumab based on its mechanism of action include serious infections and malignancy, although no increases in the rates of serious infections or malignancies have been observed. Psychiatric events including depression and suicide were observed more frequently with belimumab than with placebo, although it is unknown if belimumab treatment is associated with an increased risk for these events. Finally, mortality rates in the controlled clinical trials were low, although numerically higher in the belimumab groups (0.4% and 0.8% in the placebo and belimumab groups, respectively). Causes of death were as expected in an SLE population with active disease receiving a wide range of standard therapies, such as corticosteroids and immunosuppressants, and included infection, cardiovascular disease, and suicide.

Experience from open-label, long-term continuation trials of belimumab in SLE patients suggests prolonged treatment with belimumab remains generally well tolerated, with no apparent increase in the incidence of AEs or 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.

Belimumab in ANCA-Associated Vasculitis

Study Overview and Patient Population

Belimumab at a dose of 10 mg/kg in combination with standard SLE therapy demonstrated a statistically significant and clinically meaningful reduction in SLE disease activity versus placebo plus standard SLE therapy at Week 52 in two Phase 3 clinical studies in subjects with active, autoantibody-positive SLE.

Studies in subjects with WG and MPA have shown the need for more effective treatment for the maintenance of remission, with relapse rates with these 2 diseases ranging from 15% at 18 months (Jayne et al, 2003) to 38% at 3 years (Hiemstra et al, 2010) on azathioprine – the most effective of current therapies (Jayne et al, 2003; Pagnoux et al, 2008; Hiemstra et al, 2010).

The presence of ANCA autoantibodies in AAV implicates B cells in the pathogenesis of AAV. Further supporting a role for B cells is the fact that activated B cells are present in greater numbers in GPA subjects compared with healthy persons (Popa et al, 1999). Additionally, elevated levels of BLyS, a B cell survival factor, are found in subjects with AAV (Krumbholz et al, 2005; Nagai et al, 2011; Schneeweis et al, 2010). Together, these provide a strong pharmacologic rationale for the use of belimumab to treat AAV, since belimumab has been shown in SLE to reduce both B cells and autoantibody levels. Therefore, for the proposed study, subjects are required to have documented evidence of anti-PR3 or anti-MPO autoantibodies prior to randomization, as this population is considered the most likely to benefit from treatment with a B cell modulating agent like belimumab. This is consistent with the Phase 3 SLE results for belimumab where the subjects who benefitted from treatment were those who were antinuclear antibody (ANA/anti-dsDNA) autoantibody positive at baseline.

The fact that rituximab, a biologic therapy that targets B cells by binding to the B cell surface antigen CD20, recently showed success in inducing remission in AAV (Stone et al, 2010) and was granted approval in the US for the treatment of WG and MPA supports the rationale that belimumab, which down regulates B cells by targeting BLyS, may be useful in the treatment of this disease. Finally, limited data from the small (n = 111) subset of subjects in the Phase 3 trials of SLE who had vasculitic symptoms as part of their SLE (as assessed by the SELENA SLEDAI) showed that more subjects in the belimumab plus standard of care treatment arms had resolution of their vasculitic symptoms at Week 52 compared with subjects receiving placebo plus standard of care. Specifically, 19/36 (52.8%) and 28/38 (73.7%) of subjects in the belimumab 1 mg/kg and 10 mg/kg dose groups, respectively, had resolution of vasculitic activity at Week 52 compared with 15/37 (40.5%) of placebo subjects. Taken together, these data support the evaluation of belimumab in AAV.

The safety of the proposed study is supported by data from the Phase 2 and 3 trials in SLE in which subjects who were receiving belimumab in combination with significant background therapies, including steroids and immunosuppressants, had an adverse event profile similar to that of subjects receiving placebo plus standard therapies.

This is a Phase 3, multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen. Subjects enrolled into the study must have a clinical diagnosis of WG or MPA according to the Chapel Hill criteria and must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either CYC or RTX in the 6 months leading up to randomization. Subjects treated with 1 of the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- CYC 2 mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The doses of CYC are given as targets but may be adjusted for renal insufficiency or white cell counts as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach < 10 mg/day.

A target of 300 to 400 subjects who are within 26 weeks of starting induction therapy, achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving less than 10 mg/day prednisone (or equivalent) on 2 consecutive measurements 21 to 35 days apart will be enrolled into the study. Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter. Randomization will be performed on Day 0. Day 0 (first administration of belimumab/placebo) must occur no more than 2 weeks after confirmation of remission.

All subjects (in both the belimumab and placebo groups) will be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. Azathioprine must be initiated at any time following confirmation of remission up to and including Day 0. Patients with known intolerance to azathioprine will be excluded from the trial. Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above, a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis.

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV CYC vs. oral CYC vs. RTX). It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Refer to Section 4 of Protocol HGS1006-C1100 for a complete list of inclusion and exclusion criteria.

The primary efficacy endpoint is time from Day 0 to the first relapse, defined as at least 1 major BVAS item or a minimum total BVAS score of 6 or receipt of prohibited medications

according to the protocol. Subjects will receive study agent (belimumab/placebo) plus AZA until the results from the primary efficacy analysis are available or until they experience a flare (relapse) as defined in the primary efficacy endpoint. The database will be locked and the primary analysis will be performed after at least 66 subjects have experienced a relapse and at least 12 months have elapsed after the last subject is randomized. Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an attempt will be made to ascertain survival status at 12 months after the first dose of study agent.

If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in a 6-month open-label extension period, in which all subjects will receive 10 mg/kg belimumab IV. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety. All subjects will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent. These visits apply to subjects who have completed as well as those who have withdrawn early from the open-label extension.

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

Dose and Schedule

Investigational Study Agent (Belimumab or Placebo)

The dose and schedule of belimumab proposed for use in the ANCA-associated vasculitis study is the same dosage (10 mg/kg every 2 weeks for 3 doses and every 4 weeks thereafter) and route of administration (IV) as that approved for marketing. The belimumab BDS and FDP that will be used for this study is the same as that approved for marketing.

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

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Protocol HGS1006-C1100 Amend 02 Summary of Modifications   Belimumab

the marketed dose in general SLE, and also support its continued evaluation in combination with standard maintenance therapies in patients with WG or MPA.

The use of placebo in this trial is considered appropriate and does not put placebo patients at undue risk because all subjects in both the placebo group and the belimumab group will receive standard of care maintenance therapies for vasculitis (ie, azathioprine or methotrexate) and, if needed, subjects will receive appropriate rescue therapy in accordance with standard clinical practice as described above.

Induction and Maintenance Regimens for ANCA-Associated Vasculitis

Subjects participating in this trial will have had a moderate to severe episode of WG or MPA that was treated with high-dose corticosteroids (HDCS) and either RTX or CYC (IV or oral) to induce the remission of the disease. Subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- CYC 2mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The doses of cyclophosphamide are given as targets but may be adjusted for renal insufficiency or white cell counts as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach < 10 mg/day.

Rituximab was approved in April 2011 by the FDA for the treatment of WG and MPA. It has been used in induction of remission in AAV for a number of years, (Gorman et al, 2003, Smith et al, 2006) and 2 recent trials published in 2010 (Stone et al, 2010), demonstrated non-inferiority to induction with cyclophosphamide, the latter of these trials being used as the basis for the recent US approval. The RTX regimen specified in this vasculitis study is the same as that approved by the FDA for this indication.

Cyclophosphamide (2 mg/kg/day orally or IV 15 mg every 2 weeks for 3 doses and every 3 weeks thereafter) plus prednisone has been the standard induction regimen for WG and MPA since the early 1970s when initial work by Fauci and Wolff at the National Institutes of Health showed that this regimen induced disease remission in 12/14 patients and subsequent work showed that survival rates increased 80% using this regimen in what was previously an uniformly fatal disease (Fauci and Wolff, 1973; Fauci et al, 1983; Hoffman et al, 1992; Langford, 2011). Long term continued cyclophosphamide use, however, has been associated with significant toxicities (including infection, cystitis, cytopenias, and long term complications such as myelodysplasia and bladder cancer) and mortality (Langford, 2011).

A more recent study conducted by the European Vasculitis Group (Jayne et al, 2003) showed that after initial disease remission with cyclophosphamide and steroids, subjects could be switched to azathioprine (2 mg/kg/day) without having an increased risk of relapse compared to subjects whose remission was maintained using continued cyclophosphamide treatment. An induction regimen of CYC + prednisone followed by maintenance treatment with azathioprine is now considered the standard of care, given that administration of cyclophosphamide for longer durations does not offer an advantage from an efficacy standpoint and is associated with a greater potential for toxicity (Langford, 2011). The cyclophosphamide regimens described above are the same as those allowed in the inclusion criteria for this vasculitis study.

Once disease remission (defined as having, on 2 consecutive measurements 3 to 5 weeks apart: a BVAS v3 score of 0 and be receiving < 10 mg/day of oral prednisone [or equivalent], achieved no more than 26 weeks after the first dose of induction therapy) has been achieved, subject randomization into this protocol occurs. In this maintenance of remission trial, subjects will be randomized to receive a maintenance regimen of AZA (2 mg/kg/day) + placebo or AZA (2 mg/kg/day) + belimumab (10 mg/kg). Randomization in this protocol must occur within 2 weeks of achieving a confirmed remission and the randomization will be stratified by induction regimen.

The primary safety population for the SLE indication, including 473 subjects who were taking azathioprine as a concomitant medication at baseline, provides a substantial amount of safety data to support the conduct of the proposed trial. In this study, subjects who have a known intolerance to azathioprine will be excluded. Subjects naive to azathioprine and who experience azathioprine-related toxicity (Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT 2 times ULN, or a several gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting), following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience toxicities, a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis. The protocol instructs physicians to follow the appropriate local prescribing information for azathioprine or methotrexate (as applicable) prior to and during treatment.

Input on selection of these standard of care regimens was obtained from international experts in vasculitis, including members of the European Vasculitis Society (EUVAS) and the Vasculitis Clinical Research Consortium (VCRC), and consensus was reached that these regimens are appropriate for this international trial.

Complete details regarding the use of concurrent medications can be found in Section 5.5 of Protocol HGS1006-C1100.

Safety Considerations

An independent Data Monitoring Committee (DMC) will review safety data on an ongoing basis until the data are locked and analyzed (after which monitoring may be assumed by an internal HGS committee). The DMC will include at least 3 physicians and a statistician, none of whom are affiliated with the Sponsor. Belimumab has not yet been studied following use of IV cyclophosphamide (CYC) or rituximab (RTX); there is limited experience with the combination of belimumab and oral CYC. As an added safety precaution, initial randomization will be limited to 40 subjects per induction regimen (40 post-RTX induction and 40 post-CYC induction). The first DMC reviews will occur after the first 20 subjects per induction regimen (RTX or IV/oral CYC) have been randomized and have had a Week 8 visit. Once the first 20 subjects randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the DMC, who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with CYC. The DMC will review the data approximately every 6 months thereafter across both induction regimens. At all times the patients, study sites and sponsor will remain blinded to treatment allocation. Investigators and IRBs/IECs will be notified of the outcome of each DMC meeting.

The DMC will be notified of:

- • all unexpected causally-related SAEs that are life-threatening or result in death;
- • other unexpected causally-related SAEs;
- • all reports of serious infections and opportunistic infections, irrespective of relationship to study agent; and
- • subjects experiencing IgG < 250 mg/dL;

within protocol-specified timeframes. Based on these data, an ad hoc DMC meeting may be called at any time (see Section 8.3 of Protocol HGS1006-C1100 for additional detail regarding the DMC).

Based on the large body of safety data from SLE patients treated with belimumab and/or the mechanism of action of belimumab as a B cell immunosuppressant, anticipated potential risks of belimumab treatment in vasculitis patents include serious infusion and hypersensitivity reactions, infections, depression-related events, and malignancy. These risks are briefly reviewed here and are detailed more fully in the belimumab Investigator's Brochure. Both investigators and subjects will be appropriately informed regarding these risks. It is noted that because of the older patient population affected by this disease, the average age of subjects anticipated to participate in this study will be older than the average age of the SLE population studied to date (mean age of ~53 years at the time of diagnosis in vasculitis (Stone et al, 2010) compared with an average age of ~38 years in controlled Phase 3 studies of belimumab in SLE). As such, patients with vasculitis may be at a greater risk for infection than the SLE patients; however, the increased monitoring for infections by both the DMC (described above) and recommended to investigators (see below) will help to ensure subject safety through timely detection, treatment and reporting of infections.

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

In order to ensure subject safety with respect to infusion and hypersensitivity reactions, the protocol excludes patients with known history of allergic reactions to human or murine proteins or monoclonal antibodies. There is currently insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions to belimumab. The protocol recommends that based on clinical judgment, premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion. Antihistamine H2-receptor antagonists (eg, ranitidine) are also permitted. Belimumab/placebo will be administered by investigators/site personnel prepared to manage infusion reactions and anaphylaxis. The infusion rate may be slowed or interrupted if the subject develops an infusion reaction. Investigators/site personnel should be aware of the risk of hypersensitivity reactions, which may present as infusion reaction, and monitor subjects closely. In the event of a serious reaction, belimumab/placebo administration must be discontinued immediately and the appropriate medical therapy administered. Per protocol, subjects are to remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase and the open-label extension. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing for any untoward reactions. Beyond the first 2 infusions, subjects should be monitored during and for an appropriate period of time after infusion according to study sites' guidelines or standard operating procedure for IV infusions. Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

The protocol recommends that subjects with persistent or worsening disease should receive appropriate rescue therapy in accordance with standard clinical practice, but if exceeding what is allowed per protocol, treatment with study agent (ie, belimumab or placebo) will be discontinued and the subject will be considered as having relapsed for the primary analysis. The list of prohibited medications that results in the subjects being considered as relapsed for the primary endpoint (Protocol Section 5.5.2.1), was developed because the need for the use of these agents (eg, RTX or CYC) is indicative of treatment failure (ie, disease relapse).

Moreover, concomitant use of such medications (eg, high-dose steroids) can be associated both with potent disease-modifying activity and/or significant toxicity that may introduce

bias and confound interpretation of results. As such, no subject will be denied appropriate medical care for their condition due to their participation in this clinical study.

In addition, the Sponsor notes that although this is a placebo controlled trial, the sponsor does not consider that placebo patients are at undue risk because all subjects in both the placebo group and the belimumab group will receive standard of care maintenance therapies for vasculitis (ie, azathioprine or methotrexate) and, if needed, subjects will receive appropriate rescue therapy in accordance with standard clinical practice as described above.

Risk:Benefit Conclusions

In summary, the proposed Phase 3 study is a superiority study evaluating the safety and efficacy of belimumab for the maintenance of disease remission in patients with a clinical diagnosis of Wegener's granulomatosis or microscopic polyangiitis. The risk:benefit profile of 10 mg/kg IV belimumab in patients with active, autoantibody-positive SLE was demonstrated to be positive in the two Phase 3 SLE studies, thereby supporting its approval in Canada, the US, and the EU. Belimumab has already been shown to be effective in treating patients with active, autoantibody-positive SLE, a B cell mediated autoimmune disease. Like SLE, WG and MPA are also B cell mediated autoimmune diseases in which autoantibodies (in this case, against neutrophil components), are considered to be pathogenic (Popa et al, 1999). In each of these diseases, the general purpose of the therapy is similar – reducing disease activity by down regulating B cells (including autoreactive B cells) and reducing the level autoantibodies produced by those autoreactive B cell clones. Down regulating B cell numbers may also reduce inflammatory processes because of the role of B cells in antigen presentation. A limited amount of data from the IV Phase 3 studies suggests that belimumab may reduce vasculitic symptoms.

There are potential risks associated with belimumab treatment including serious infusion and hypersensitivity reactions, infections, depression-related events, and malignancy; however, in view of the serious and potentially life threatening nature of disease flares in WG and MPA, it is believed that the overall risk:benefit analysis for belimumab in the maintenance of remission in WG and MPA is favorable, especially in view of the nature of the trial as a superiority trial over a current standard of care regimen.

Protocol Amendment 01, 22 June 2012
Protocol Number: HGS1006-C1100

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The protocol has been modified to further define allowable/prohibited doses of corticosteroids that can be given for vasculitis and for reasons other than vasculitis. It is now specified that IV corticosteroid pulses for vasculitis at any dose are prohibited and use of such will result in the subject being considered as relapsed for the primary endpoint; it is considered that subjects requiring IV corticosteroid pulses are having sufficient disease activity to qualify as having relapsed. In relation to this, it is now clarified that IV steroid pulses > 125 mg prednisone (or equivalent) are prohibited for reasons other than vasculitis and such use will also result in the subject being considered a treatment failure. Importantly, it is also now stated that use of high dose steroids (ie, average daily dose of > 20 mg/day prednisone or equivalent for ≤ 14 days or IV corticosteroid pulses ≤ 125 mg prednisone or equivalent) for non vasculitis reasons may only be given to a subject 1 time in any 365 day period without the subject being considered a treatment failure. These modifications to the protocol will prevent uncontrolled use of oral and IV pulse corticosteroids that could confound the interpretation of study results.
2. A statement has been added to clarify that the protocol-defined induction regimens for cyclophosphamide are given as treatment targets but that they may be adjusted to account for renal insufficiency or reduced white blood cell counts as dictated by local standard of care practices.
3. A subgroup analysis by duration of IV corticosteroid pulse used for induction (1 day vs. > 1 day) has been added.
4. The language regarding the recommended HDCS tapering to reach the entry criteria of < 10 mg/day has been corrected from the previously written < 10 mg/kg.
5. The dose of methotrexate to be used in case of azathioprine toxicity has been clarified to be a target dose, to allow for flexibility in individual practice. A minimum dose of methotrexate (no less than 10 mg/week) is also specified, to ensure subjects are receiving a sufficient and relatively consistent therapy. This change also ensures the guidance given for methotrexate is consistent with that given for azathioprine.
6. Vital signs have been added to the listing of screening procedures to match the study calendar footnote.
7. The visit windows for the 8 and 12 week visits in Study Calendar 6-1 have been corrected to +/- 7 days rather than +/- 3 days.
8. Serum IgG has been added to the 8 Week Follow-up visits in Study Calendars 6-1 and 6-2. This was omitted in error in amendment 00 of the protocol.
9. Footnote number 12 in Study Calendar 6-1 and footnote number 8 in Study Calendar 6-2 have been revised to correspond with Section 7.2 of the protocol.

10. Dysmorphic RBC analysis of Urine has been removed from the laboratory tests. This data will not be provided by the Central Lab contracted for this study.

Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment: 00
Date: 07 March 2012

Modified to:

Protocol Amendment **01**
Date: **22 June** 2012

Study Synopsis, Study Design and Schedule:
Section 3.1 Basic Design Characteristics:

Formerly:

Subjects enrolled into the trial must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either cyclophosphamide (CYC) or rituximab (ie, induction therapy) in the 6 months leading up to randomization. Only subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course rituximab (RTX) administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HCDS) OR
- Cyclophosphamide 2mg/kg/day orally plus HDCS OR
- Cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach < 10 mg/kg.

Modified to:

Subjects enrolled into the trial must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either cyclophosphamide (CYC) or rituximab (ie, induction therapy) in the 6 months leading up to randomization. **Subjects** treated under the following induction regimens will be eligible for participation in the study:

- A single course rituximab (RTX) administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (**HDCS**) OR
- Cyclophosphamide 2mg/kg/day orally plus HDCS OR
- Cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The doses of cyclophosphamide are given as targets but may be adjusted for renal insufficiency or white cell counts as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach < 10 mg/**day**.

Section 5.5.1 Prohibited Medications and Therapies that Result in Treatment Failure

Formerly:

Subjects who start prohibited medication or therapies at any time during the double-blind phase will be considered as having relapsed as of the time of receipt of the prohibited medication, and treatment with study agent will be discontinued. However, the subject will continue to be followed for survival through at least 12 months after randomization. The following medications and therapies are prohibited during the study:

- Other immunomodulatory investigational agents (biologic or non-biologic);
- Rituximab;
- Cyclophosphamide;
- Other immunosuppressive agents (eg, cyclosporine) with the exception of methotrexate for AZA intolerance described in Section 5.5.3;
- Corticosteroids for vasculitis at doses > 20 mg/day prednisone (or equivalent);
- Corticosteroids at an average daily dose of > 20 mg/day prednisone (or equivalent) for > 14 days for any reason (average daily dose is the sum of the dose over 7 consecutive days divided by 7);
- IV corticosteroid pulses > 125 mg prednisone (or equivalent); and
- Plasmapharesis.

Modified to:

Subjects who start prohibited medication or therapies at any time during the double-blind phase will be considered as having relapsed as of the time of receipt of the prohibited medication, and treatment with study agent will be discontinued. However, the subject will continue to be followed for survival through at least 12 months after randomization. The following medications and therapies are prohibited during the study:

- Other immunomodulatory investigational agents (biologic or non-biologic);
- Rituximab;
- Cyclophosphamide;
- Other immunosuppressive agents (eg, cyclosporine) with the exception of methotrexate for AZA intolerance described in Section 5.5.3;
- Corticosteroids for vasculitis:
  - doses > 20 mg/day prednisone (or equivalent)**, or**
  - **IV corticosteroid pulses at any dose;**
- **Corticosteroids for reasons other than vasculitis:**
  - at an average daily dose of > 20 mg/day prednisone (or equivalent) for > 14 days **where the** average daily dose is **calculated as** the sum of the dose over 7 consecutive days divided by 7**, or**
  - IV corticosteroid pulses > 125 mg prednisone (or equivalent)
  Note: Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or IV corticosteroid pulses ≤ 125 mg prednisone (or equivalent) for reasons other than vasculitis cannot be given more than once in any 365 day period (See also Section 5.5.3).
- Plasmapharesis.

5.5.3 Allowable Medications

Formerly:

The use of stable baseline dose regimens of corticosteroids (< 10 mg/day prednisone or equivalent) are permitted over the course of the trial. Inhaled corticosteroids for asthma, or topical corticosteroids for atopic dermatitis are also permitted.

Modified to:

The use of stable baseline dose regimens of corticosteroids (< 10 mg/day prednisone or equivalent) is permitted over the course of the trial. Inhaled corticosteroids for asthma, or topical corticosteroids for atopic dermatitis are also permitted. **Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or an IV corticosteroid pulse up to 125 mg prednisone (or equivalent) are permitted for reasons other than vasculitis (eg. acute allergic reaction), but a subject cannot receive more than 1 such corticosteroid regimen in any 365 day period (See also Section 5.5.3).**

5.5.3.1 Azathioprine and Methotrexate, - Second paragraph

Formerly:

Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times the ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be

permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above a switch to methotrexate at doses of up to 25mg/week as an alternative to azathioprine will be permitted. These subjects will be included in the primary analysis.

Modified to:

Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times the ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above a switch to methotrexate **at a target dose** of 25mg/week **(and no less than 10 mg/week)** as an alternative to azathioprine will be permitted. These subjects will be included in the primary analysis.

Study Procedures:
6.1   Screening Procedures; Fourth Bullet

Formerly:

Complete physical examination, including height, weight.

Modified to:

Complete physical examination, including height, weight **and vital signs**.

Table 6-1 Study Calendar:
Study Visit Window for Week 8 and Week 12

Formerly:

$\pm$ 3 days

Modified to:

$\pm$ **7** days

Table 6-1 and Table 6-2 Study Calendars:
Serum IgG – 8 Week Follow-up Visit

Formerly:

Serum IgG was not assessed at this time point

Modified to:

Serum IgG is marked "**X**" as required at this visit.

Table 6-1; Footnote number 12
Table 6-2; Footnote number 8

Formerly:

In subjects who discontinue study agent prior to relapse/flare all AEs and SAEs will be reported on the AE eCRF through 8 weeks following administration of the last dose of study agent. After this time, all SAE, regardless of relationship to study drug, will be collected until relapse or the study is analyzed for the primary endpoint and study sites are informed that SAE data collection can cease, whichever occurs first.

Modified to:

In subjects who discontinue study agent all AEs and SAEs will be reported on the AE eCRF through 8 weeks following administration of the last dose of study agent. After this time, all SAE, regardless of relationship to study drug, will be collected until relapse or the study is analyzed for the primary endpoint, whichever occurs first.

Subgroup Analysis:
8.5.2.1 Ninth Bullet added

Formerly:

Not listed.

Modified to:

- **Duration of IV corticosteroid pulse used for induction (1 day vs. > 1 day)**

Appendix 6 Laboratory Tests

Formerly:

Occult blood microscopic examination including Dysmorphic RBC;

Modified to:

[Text deleted]

Sponsor Signatory: **Signature:** **Date:**

PPD

David A. Roth, MD, MSCE 21-Jul-2018
Director, Global Clinical
R&D,
Immuno-Inflammation
Therapy Area

CLINICAL PROTOCOL HGS1006-C1100
Protocol Amendment: 04
Date: 26 February 2015
EudraCT 2011-004569-33
Local Amendment 01 for Belgium, Date: 06 July 2015

Amend 01
22Jun12

Amend 02
25Apr13

Amend 03
04Feb14

Amend 04
26Feb15

Am01/Belgium
06Jul15

TITLE OF STUDY:

A Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

STUDY SPONSOR: Human Genome Sciences, Inc.
14200 Shady Grove Road
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Confidentiality

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Revision Chronology for HGS1006-C1100 (BEL115466)

	Date	**Document***
Global	07 March 2012	Original
Global	22 June 2012	Amendment No 01
Local	29 January 2013	Addendum 01 for Sweden
Local DNG2013N160488_01	31 January 2013	Addendum 01 for Ireland
Global DNG2013N167980_00	25 April 2013	Amendment No 02
Global DNG2013N167980_01	04 February 2014	Amendment No 03
Local DNG2014N217970_01	01 October 2014	Local Amendment 01 for France
Local DNG2014N217970_02	03 February 2015	Local Amendment 02 for France
Global DNG2013N167980_02	26 February 2015	Amendment No 04
Local 2015N245521_00	06 July 2015	Local Amendment 01 for Belgium

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

2015N245521_00

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Clinical Protocol HGS1006-C1100 Amend 04 (Local 01 Belgium)   Belimumab

Investigator Agreement

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

Principal Investigator:

_____

Signature   *Date*

_____

Name (please type or print)

_____

Institution

_____

Address

Study Synopsis

Study Number: HGS1006-C1100

Title of the Study:

A Multi-Center, Multinational, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis Amend 04 26Feb15

Clinical Development Phase: 3

Objectives:

- To evaluate the efficacy of belimumab in the maintenance of remission following a standard induction regimen in subjects with Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA).
- To evaluate the safety of belimumab in subjects with WG or MPA.

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

1. Are at least 18 years of age.
2. Have a clinical diagnosis of Wegener's granulomatosis (WG) or a diagnosis of microscopic polyangiitis (MPA) according to the Chapel Hill criteria (Appendix 1 and Appendix 2).
3. In the 26 weeks prior to randomization (Day 0), had an episode of moderately to severely active WG or MPA requiring treatment under one of the following induction regimens: Amend 03 04Feb14

   A single course of rituximab administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
   A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR
   cyclophosphamide 2 mg/kg/day orally plus HDCS OR
   cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.
   [The cyclophosphamide dosing regimens are provided as targets but may be adjusted for older age, obesity, renal insufficiency, leukopenia, or other toxicities as dictated by local practice.]
4. Have documented evidence of either anti-proteinase 3 (anti-PR3) or anti-myeloperoxidase (anti-MPO) prior to Day 0.
5. Have a Birmingham Vasculitis Activity Score (BVAS v.3 [Appendix 3]) of 0 and be receiving ≤ 10 mg/day oral prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart, between 6 and 26 weeks after the first dose of induction therapy Amend 03 04Feb14

(either CYC or RTX, as defined in Section 3.1). A minimum 6 week period should elapse between initiation of induction therapy and randomization.

6. Subjects receiving non-systemic corticosteroids for reasons other than vasculitis must be on a stable regimen prior to randomization.

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

   Not pregnant or nursing;
   Of non-childbearing potential (ie, women who had a hysterectomy, are postmenopausal which is defined as 12 consecutive months with no menses without an alternative medical cause, have both ovaries surgically removed or have current documented tubal ligation or other permanent sterilization procedure); or

   Of childbearing potential (ie, women with functional ovaries and no documented impairment of oviductal or uterine function that would cause sterility). This category includes women with oligomenorrhoea [even severe], women who are peri-menopausal or have just begun to menstruate. These women must have a negative serum pregnancy test at screening, and agree to 1 of the following:
     o Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent; or
     o Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:
       o Implants of levonorgestrel or etonogestrel;
       o Injectable progesterone;
       o Transdermal contraceptive patch
       o Any intrauterine device (IUD) with a documented failure rate of less than 1% per year;
       o Oral contraceptives (either combined or progesterone only);
       o Ethinyl estradiol/Etonogestrel vaginal ring
       o Double barrier method: Condom and Occlusive cap (diaphragm or cervical/vault caps) with spermidical foam/gel/film/cream/suppository; or
       o 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.

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

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

1. Co-existence of other multisystem autoimmune diseases.

2. Known intolerance or contraindications to azathioprine (AZA); and known intolerance or contraindications to methotrexate where methotrexate is being considered as an alternative to AZA for maintenance therapy.

3. Have received treatment with a B-cell directed therapy (other than rituximab), for example anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], anti-CD40L antibody [BG9588/ IDEC-131], BLyS-receptor fusion protein [BR3], LY2127399, TACI-Fc, or belimumab at any time.

4. Have required 3 or more courses of systemic corticosteroids for concomitant conditions not related to their vasculitis (eg, asthma, atopic dermatitis) within 364 days of Day 0. (Topical or inhaled steroids are permitted.)

5. Have received a non-biologic or biologic investigational agent within 60 days or 5 half-lives of the agent (whichever is longer) of Day 0.

6. Have received a live vaccine within 30 days of Day 0.

7. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to vasculitis (ie, cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious disease) which, in the opinion of the principal investigator, could confound the results of the study or put the subject at undue risk.

8. Have a planned surgical procedure or a history of any other medical disease (eg, cardiopulmonary), laboratory abnormality, or condition (eg, poor venous access) that, in the opinion of the principal investigator, makes the subject unsuitable for the study.

9. 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.

10. Have required management of acute or chronic infections, as follows:

    Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, aspergillosis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
    Hospitalization for treatment of infection within 60 days of Day 0.
    Use of parenteral (intravenous, subcutaneous or intramuscular) antibiotics, antibacterials, antivirals, anti-fungals, or anti-parasitic agents within 60 days of Day 0.

11. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 0.

12. Have a historically positive HIV test or test positive at screening for HIV.   Amend 02 25Apr13

13. Hepatitis B: Serologic evidence of Hepatitis B (HB) infection based on the results of testing for HBsAg, anti-HBc and anti-HBs as follows: Amend 02 25Apr13

    Patients positive for HBsAg are excluded.
    Patients negative for HBsAg and anti-HBc antibody but positive for anti-HBs antibody and with no history of Hepatitis B vaccination are excluded.
    Patients negative for HBsAg but positive for both anti-HBc and anti-HBs antibodies are excluded.
    Patients negative for HBsAg and anti-HBs antibody but positive for anti-HBc antibody are excluded.

14. Hepatitis C: Positive test for Hepatitis C antibody confirmed on a subsequent blood sample by RNA-PCR assay. Subjects who are positive for Hepatitis C antibody and negative when the Hepatitis C RNA-PCR assay is performed on a subsequent sample will   Amend 02 25Apr13

be eligible to participate. Subjects who are positive for Hepatitis C antibody and have a positive result for the HCV when the Hepatitis C RNA-PCR assay is performed on the subsequent sample will not be eligible to participate.

15. Have an IgA deficiency (IgA level < 10 mg/dL).

16. Have a Grade 3 or greater laboratory abnormality based on the protocol DMID toxicity scale, unless considered by the investigator to be related to the underlying disease or induction therapy.

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

18. Subjects who have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months and/or any suicidal ideation of type 4 or 5 on the C-SSRS (Refer to Appendix 8 for C-SSRS) in the last 2 months or who in the investigator's opinion, pose a significant suicide risk.

19. Subjects who have abnormal liver function tests defined as follows: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\geq$ 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%).

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Study Design and Schedule:

This is a multi-center, multi-national, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

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Subjects enrolled into the trial must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either cyclophosphamide (CYC) or rituximab (ie, induction therapy) in the 6 months leading up to randomization. Subjects treated under the following induction regimens will be eligible for participation in the study:

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- A single course rituximab (RTX) administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR

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- A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR

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- Cyclophosphamide 2mg/kg/day orally plus HDCS OR
- Cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

[The cyclophosphamide dosing regimens are provided as targets but may be adjusted for older age, obesity, renal insufficiency, leukopenia, or other toxicities as dictated by local practice.]

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For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 0.5-1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ≤ 10 mg/day. As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.

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Subjects who are between 6 and 26 weeks of starting induction therapy, achieve a BVAS v.3 score of 0 (Appendix 4), and are receiving ≤ 10 mg/day prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart may be enrolled into the study. A minimum 6 week period should elapse between initiation of induction therapy and randomization. Randomization will be performed on Day 0. A schematic of the study design is shown below.

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All randomized subjects should be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. Azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine should not be initiated any later than Day 0. Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). Belimumab or placebo will be supplied by the sponsor during this double-blind treatment phase. It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, 28, and every 28 days thereafter.

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Initial randomization will be limited to 40 subjects per induction regimen (40 post-RTX induction and 40 post-CYC induction). Once the first 20 patients randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the independent data monitoring committee (DMC), who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with CYC. At all times the sites and sponsor will remain blinded to treatment allocation.

Subjects will receive study agent (belimumab/placebo) plus AZA until the study has completed or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see below). The double-blind phase of the study will complete, the database will be locked and the primary analysis will be performed when 12 months have elapsed after the last subject is randomized.

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In consultation with the investigating physician, subjects participating in the double-blind period of the trial will have the option to continue to receive treatment with belimumab in a 6-month open label extension phase. The criteria for entry into the extension phase of the study are: (1) the safety profile of belimumab is considered to be acceptable, based on ongoing

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IDMC data reviews of the safety data, and other relevant safety data sources; (2) the risk-benefit profile for continuing treatment with belimumab must be favorable in the opinion of the investigator; (3) the subject will have completed the double-blind treatment period of the trial without having relapsed (as defined in the primary endpoint); (4) a favorable opinion has been obtained from the local ethics committee or IRB with respect to continuation of belimumab treatment. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months and this will be supplied by the sponsor.

Following completion of the study and, where applicable, completion of the 6-month open-label extension phase, subjects will not receive any additional treatment supplied by the sponsor. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

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Subjects who discontinue study agent prior to relapse/flare (as defined below) are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an attempt will be made to ascertain survival status at 12 months after the first dose of study agent.

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Schematic of study design:

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Efficacy Endpoints and Analysis:

Primary Efficacy Endpoint:

The primary efficacy endpoint is time from Day 0 to the first relapse, defined as:

- At least 1 major BVAS item (Appendix 4) OR
- A minimum total BVAS score of 6 (Appendix 4) OR
- Receipt of prohibited medications (as defined in Section 5.5.1).

Major Secondary Efficacy Endpoint:

- Time from Day 0 to the first major relapse (defined as experiencing at least 1 major BVAS item, see Appendix 4).

Other efficacy endpoints are described in Section 8.5.4.

Sample Size Considerations:

Approximately 100 subjects will be randomized. The sample size has been determined based on the feasibility of enrolling patients into the study within a reasonable time-frame. The sample size was not based on statistical considerations and the analysis of primary and secondary endpoints will be exploratory in nature. The primary efficacy analysis will be performed after 12 months have elapsed following randomization of the last subject.

Although the sample size is based on feasibility, the minimal detectable effect has been determined. Assuming an observed relapse rate at 18 months of 20% in the placebo group, a relapse rate of ≤7.0% on belimumab (hazard ratio ≤0.32) would be statistically significant (p<0.05) in a study of 100 subjects (50 per arm).

Analysis of Primary Efficacy Endpoint:

The primary efficacy analysis will compare the time to first relapse from Day 0 between the placebo/azathioprine group and the belimumab/azathioprine combination group using a Cox proportional hazards model, adjusted for ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide). However, the adjustment of induction regimen will be changed to rituximab vs. IV and/or oral cyclophosphamide if the number of events (relapse) is less than 5 in subjects using oral cyclophosphamide or IV cyclophosphamide. For any subject who does not experience a relapse, the time to first relapse will be censored at the time of the subject's last assessment.

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The primary efficacy analysis will be performed after 12 months have elapsed following randomization of the last subject.

Analysis of Major Secondary Efficacy Endpoints:

The analysis of the major secondary efficacy endpoint will be performed using the same method described for the primary efficacy analysis, but censoring subjects who receive any prohibited medication prior to an observation of any major BVAS item.

Safety Endpoints and Analysis:

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

Adverse events of special interest that will be analyzed in this protocol include: all-cause mortality; serious and/or severe infections; opportunistic infections; infusion reactions including hypersensitivity reactions; malignant neoplasms; selected serious psychiatric events; suicidality assessment (Appendix 8); and immunogenicity.

An independent Data Monitoring Committee (DMC) will review safety data on an ongoing basis until the data are locked and analyzed. The DMC will include at least 3 physicians and a statistician, none of whom are affiliated with the Sponsor. The first DMC reviews will occur after the first 20 subjects per induction regimen (RTX or IV/oral CYC) have been randomized and have had a Week 8 visit. Once the first 20 subjects randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the DMC, who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with IV or oral CYC. The DMC will review the data approximately every 6 months thereafter across both induction regimens. At all times the sites and sponsor will remain blinded to treatment allocation. The DMC will monitor this trial until the data are locked, unblinded, and analyzed for the primary efficacy outcome, after which time monitoring may be assumed by an internal Human Genome Sciences (HGS) committee. Investigators and IRBs/ECs will be notified of the outcome of each DMC meeting.

PK Endpoints and Analysis:

Serum samples will be collected from all randomized subjects who receive a dose of study agent during the study and analyzed to determine serum belimumab concentrations. Serum belimumab concentration data will be used in a population PK analysis, which will be reported separately.

Immunogenicity:

Serum samples for the measurement of anti-belimumab antibodies will be obtained from all subjects before administration of study agent on Day 0, Week 8, Week 24, Week 48 and Exit/8-week Follow-up. Additionally, samples will be obtained from subjects at Weeks 24 and 48 during additional years. For any subject who had a positive antibody response at the 8-week follow-up visit (or last study visit at which immunogenicity was assessed if 8-week

follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or after completion and/or unblinding of the study, whichever is later.

Biological Markers and Autoantibodies:

Pharmacogenetic sampling (in consenting subjects) will be taken once during the course of this study (see Appendix 9).

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

- Anti-neutrophil cytoplasmic antibody (ANCA: antiPR3, anti-MPO)
- Serum complement (C3, C4)
- Serum immunoglobulin isotypes (IgA, IgM, IgG)
- C-reactive Protein (CRP)
- Erythrocyte sedimentation rate (ESR)
- Urinary protein: urinary creatinine ratio
- BLyS protein (Day 0 only)
- FACS of peripheral lymphocytes

Study Calendar

See Section 6 for a calendar of study visits and assessments.

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List of Abbreviations

AAV   ANCA-associated vasculitis
aCL   anticardiolipin
ACR   American College of Rheumatology
AE   adverse event
ALT   alanine aminotransferase
ANA   anti-nuclear antibody
ANCA   anti-neutrophil cytoplasmic antibodies
Anti-dsDNA   anti-double-stranded DNA
Anti-MPO   anti- myeloperoxidase
Anti-PR3   anti-proteinase 3
Anti-RNP   anti-ribonucleoprotein
Anti-Sm   anti-Smith antibody (see Sm)
aPTT   activated partial thromboplastin time
AST   aspartate aminotransferase
AUC   area under the serum drug concentration-time curve
AZA   azathioprine
BAFF   B Cell Activating Factor belonging to the TNF Ligand Family
BILAG   British Isles Lupus Assessment Group of SLE Clinics
BLyS   B lymphocyte Stimulator
BR3   BLyS-receptor fusion protein
BUN   blood urea nitrogen
BVAS   Birmingham Vasculitis Activity Score
ºC   degrees Celsius
C3   Complement Factor 3
C4   Complement Factor 4
C-ANCA   Cytoplasmic antineutrophil cytoplasmic antibodies
CHCC   Chapel Hill consensus Conference
Chem   chemistry
Cl_{cr} creatinine clearance
Coag   Coagulation
CPK   creatine phosphokinase
CRF   case report form
CRO   Contract Research Organization
CRP   C-Reactive Protein
CSS   Churg-Strauss Syndrome
C-SSRS   Columbia-Suicide Severity Rating Scale
CYC   cyclophosphamide
dL   deciliter
DMC   Data Monitoring Committee
DMID   Division of Microbiology & Infectious Diseases
DNA   deoxyribonucleic acid
dsDNA   double stranded DNA
DSM   Diagnostic and Statistical Manual

ECG	electrocardiogram
ECL	electrochemiluminescence
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
ESR	erythrocyte sedimentation rate
EU	Europe
FACS	florescence activated cell sorting
Fc	immunoglobulin constant region (fragment crystallizable)
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GPA	Granulomatosis with polyangiitis
HB	hepatitis B
HBsAg	hepatitis B surface antigen
HBc	hepatitis B core
HDCS	high dose corticosteroids
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HGS	Human Genome Sciences, Inc.
HIV	human immunodeficiency virus
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IM	intramuscular
INR	International Normalized Ratio
INN	international nonproprietary Name
IRB	Institutional Review Board
ITT	intention to treat
IUD	intrauterine device
IV	intravenous
IVIG	intravenous immunoglobulin
IWRS	Interactive Web Response System
kDa	kilodalton
kg	kilogram
LDH	lactate dehydrogenase
m^2	meters squared
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MPA	microscopic polyangiitis
MPO	myeloperoxidase

MTX	methotrexate
n	number
µg	microgram
mg	milligram
mL	milliliter
OD	optical density
PAN	polyarteritis nodosa
P-ANCA	perinuclear antineutrophil cytoplasmic antibodies
PGx	pharmacogenetics
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PR3	proteinase 3
PSE	protocol specified events
PSRHQ	possible suicidality related history questionnaire
PSRQ	possible suicidality related questionnaire
PT	prothrombin time
PTT	partial thromboplastin time
RA	rheumatoid arthritis
RBC	red blood cell
RF	rheumatoid factor
RTX	rituximab
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SLE	Systemic lupus erythematosus
SOC	System Organ Class
SRI	SLE responder index
SWFI	sterile water for injection
$t_{1/2,term}$	terminal half-life
TACI	transmembrane activator and calcium-modulator and cyclophilin ligand interactor
TEN	toxic epidermal necrolysis
TNFSF13B	Tumor Necorsis Factor Superfamily Member 13 B
TPMT	thiopurine methyltransferase
ULN	upper limits of normal
USA	United States of America
USAN	United States Adopted Name
VDI	Vasculitis Damage Index
WBC	white blood cell
WG	Wegener's Granulmatosis (Granulomatosis with polyangiitis)

1 Background

1.1 Disease Background

The systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies including infective and drug-induced causes and can be either primary or secondary to other diseases such as SLE. A subset of the primary small vessel vasculitides: Wegener's granulomatosis (also commonly referred to as granulomatosis with polyangiitis [GPA]), microscopic polyangiitis and Churg-Strauss syndrome (CSS), are characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) (Jennette and Falk, 1997). ANCA-associated vasculitides (AAV) are multisystem diseases with a broad range of manifestations from cutaneous ulcers, scleritis, pericarditis to life-threatening manifestations such as lung hemorrhage and renal failure. All 3 forms of AAV share the characteristic of systemic necrotizing vasculitis; WG and CSS are further characterized by granuloma formation. Historically, ANCA have been classified on the basis of their staining patterns in immunofluoresence assays as either cytoplasmic (C-ANCA) or perinuclear (P-ANCA). It is now recognized that in AAV, C-ANCA is usually directed against proteinase 3 (PR3), and P-ANCA is generally directed against myeloperoxidase (MPO), both of which are enzymes that are abundant in the granules of neutrophils (Jennette and Falk, 1997; Merkel et al, 1997). Anti-PR3 antibodies are generally associated with WG, while anti-MPO autoantibodies are more common in MPA and CSS. Anti-PR3 antibodies are associated with increased morbidity and mortality compared to anti-MPO (Hogan et al, 1996; Franssen et al, 1998). The most widely used classification criteria for diagnosing the 3 types of AAV are those published by the American College of Rheumatology (ACR) for WG and CSS (Leavitt et al, 1990 and Masi et al, 1990, respectively), and that published by the Chapel Hill Consensus Conference (CHCC) for MPA (Jennette et al, 1994; Jennette et al, 2013). Of note, none of these diagnostic criteria incorporate the measurement of ANCA. The Chapel Hill criteria for WG can be found in Appendix 1 and for MPA in Appendix 2.

The precise epidemiology of these diseases is uncertain as early studies did not utilize the same classification criteria as later ones (Koldingsnes and Nossent, 2008; Watts et al, 2007; Mahr, 2009). In the case of MPA, in particular, epidemiological studies are confounded by its original inclusion as a form of polyarteritis nodosa (PAN). Utilising the ACR or CHCC criteria, prevalence rates range from 5-16/100000 for WG, 2.5-9.4/100000 for MPA, and 0.4-1.4/100000 for CSS making the latter the least prevalent of the three by some margin (Koldingsnes and Nossent, 2008). In the US, the prevalence rates of WG range from 2.6-9/100000 (Zeft et al, 2005; Mahr et al, 2006). AAV are extremely rare in childhood with peak age of onset in those aged 65 to 74 years (Ntatsaki et al, 2010), with other small vessel vasculitides being the major concern in childhood (Brogan et al, 2010).

Current therapy is usually determined by severity of the disease, with more severe forms warranting more aggressive approaches. These usually involve an initial remission induction regimen of high dose corticosteroid administered with either cyclophosphamide or rituximab followed by a remission maintenance period usually with azathioprine (Stone et al, 2010; Bosch et al, 2007; Jayne et al, 2003). Minor manifestations are usually treated with low dose

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corticosteroid administered with either azathioprine or methotrexate (Belmont, 2006). Even with recent treatment advances the morbidity and mortality of patients with AAV remains unacceptably high (Drooger et al, 2009).

The Birmingham Vasculitis Activity Score (BVAS) was developed and validated as a tool to measure disease activity (Luqmani et al, 1994). It has been modified to form the BVAS/WG (Stone et al, 2001) and updated most recently with the validation of version 3 of the instrument, also known as BVAS 2003 (Mukhtyar et al, 2008, Appendix 3). In its current form it is a list of 56 items which are considered to be manifestations of vasculitis. A weighted numerical score is attached to each item to reflect the importance of each manifestation. The items are grouped by organ systems, and each organ system has a maximum or 'ceiling' score to reflect the relative importance of the organ system (Mukhtyar et al, 2008). The tool also makes a distinction between new or worsening disease and persistent disease with new or worsening attracting higher scores.

1.2   Study Agent Background

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

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

1.3   Clinical Experience

1.3.1 Belimumab Administered Intravenously

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

Phase 3 studies of belimumab in SLE were completed in 2009 and 2010 and formed the basis of IV belimumab in the US, Canada and EU. The Phase 3 trials included 1,684 subjects where belimumab 10 mg/kg plus standard therapy demonstrated superiority over placebo plus standard therapy in reduction in disease activity as measured by the SLE responder index (SRI) with an acceptable safety profile. The primary safety population supporting approval also included data from a Phase 2 study in 449 subjects with SLE. Evidence of benefit in other clinical measures such as reductions in disease activity as measured by SELENA SLEDAI, severe flare, and reduced steroid use was also observed. Treatment with belimumab plus standard of care was generally well tolerated, with rates of adverse events (AEs), severe AEs, serious AEs, AEs leading to discontinuation and serious/severe infections generally comparable to the rates observed in the placebo plus standard of care group. Mortality rates in

the controlled clinical trials were low, although numerically higher in the belimumab groups: 0.4% and 0.8% in the placebo and belimumab groups, respectively. Causes of death were as expected in an SLE population with active disease receiving a wide range of standard therapies, such as steroids and immunosuppressants, and included infection, cardiovascular disease, and suicide. Serious infections were observed in 5.2% and 6.0% of subjects receiving placebo and belimumab, respectively. The rate of malignancy (excluding non-melanoma skin cancer) was the same between the placebo and belimumab groups at 0.4%; however as with other immunomodulating agents, the mechanism of action of belimumab could increase the risk for the development of malignancies. Hypersensitivity and infusion reactions were observed. Anaphylaxis was also observed, though rare (< 1%). Depression-related events, common in patients with SLE, were observed more frequently with belimumab than with placebo; it is unknown if belimumab treatment is associated with an increased risk for these events. The most commonly-reported adverse reactions, occurring in $\geq 5\%$ of subjects in clinical trials were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis.

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

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

A benefit-risk evaluation of belimumab in the context of the present study is provided in Appendix 12 of this protocol.

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1.4 Rationale for the Study

Studies in subjects with WG and MPA have shown the need for more effective treatment for the maintenance of remission, with relapse rates with these 2 diseases ranging from 15% at 18 months (Jayne et al, 2003) to 38% at 3 years (Hiemstra et al, 2010) on azathioprine – the most effective of current therapies (Jayne et al, 2003; Pagnoux et al, 2008; Hiemstra et al, 2010).

The presence of ANCA autoantibodies in AAV implicates B cells in the pathogenesis of AAV. Further supporting a role for B cells is the fact that activated B cells are present in greater numbers in GPA subjects compared with healthy persons (Popa et al, 1999). Additionally, elevated levels of BLyS, a B cell survival factor, are found in subjects with AAV (Krumbholz et al, 2005; Nagai et al, 2011; Schneeweis et al, 2010). Together, these provide a strong pharmacologic rationale for the use of belimumab to treat AAV, since belimumab has been shown in SLE to reduce both B cells and autoantibody levels.

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The fact that rituximab, a biologic therapy that targets B cells by binding to the B cell surface antigen CD20 (Dass et al, 2008; Wang et al 2008), recently showed success in inducing remission in AAV (Stone et al, 2010) and was granted approval for the treatment of WG and MPA supports the rationale that belimumab, which down regulates B cells by targeting BLyS, may be useful in the treatment of this disease. Finally, limited data from the small (n = 111) subset of subjects in the Phase 3 trials of SLE who had vasculitic symptoms as part of their SLE (as assessed by the SELENA SLEDAI) showed that more subjects in the belimumab plus standard of care treatment arms had resolution of their vasculitic symptoms at Week 52 compared with subjects receiving placebo plus standard of care. Specifically, 19/36 (52.8%) and 28/38 (73.7%) of subjects in the belimumab 1 mg/kg and 10 mg/kg dose groups, respectively, had resolution of vasculitic activity at Week 52 compared with 15/37 (40.5%) of placebo subjects. Taken together, these data support the evaluation of belimumab in AAV.

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2 Study Objectives

2.1 Primary Objective

1. To evaluate the efficacy of belimumab in the maintenance of remission following a standard induction regimen in subjects with Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA).
2. To evaluate the safety of belimumab in subjects with WG or MPA.

3 Study Design

3.1 Basic Design Characteristics

This is a multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen. Subjects enrolled into the trial must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either cyclophosphamide (CYC) or rituximab (ie, induction therapy) in the 6 months leading up to randomization. Subjects treated under the following induction regimens will be eligible for participation in the study:

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- A single course rituximab (RTX) administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval plus HSCS OR
- Cyclophosphamide 2mg/kg/day orally plus HDCS OR
- Cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

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[The cyclophosphamide dosing regimens are provided as targets but may be adjusted for older age, obesity, renal insufficiency, leukopenia, or other toxicities as dictated by local practice.]

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For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 0.5-1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ≤ 10 mg/day. As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.

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Subjects who between 6 and 26 weeks of starting induction therapy, achieve a BVAS v.3 score of 0 (Appendix 4) and are receiving ≤ 10 mg/day oral prednisone (or equivalent) on 2 consecutive visits at least 14 days apart may be enrolled into the study. A minimum 6 week period should elapse between initiation of induction therapy and randomization. Randomization will be performed on Day 0. A schematic of the study design is shown in Figure 1.

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Figure 1 Schematic of study design

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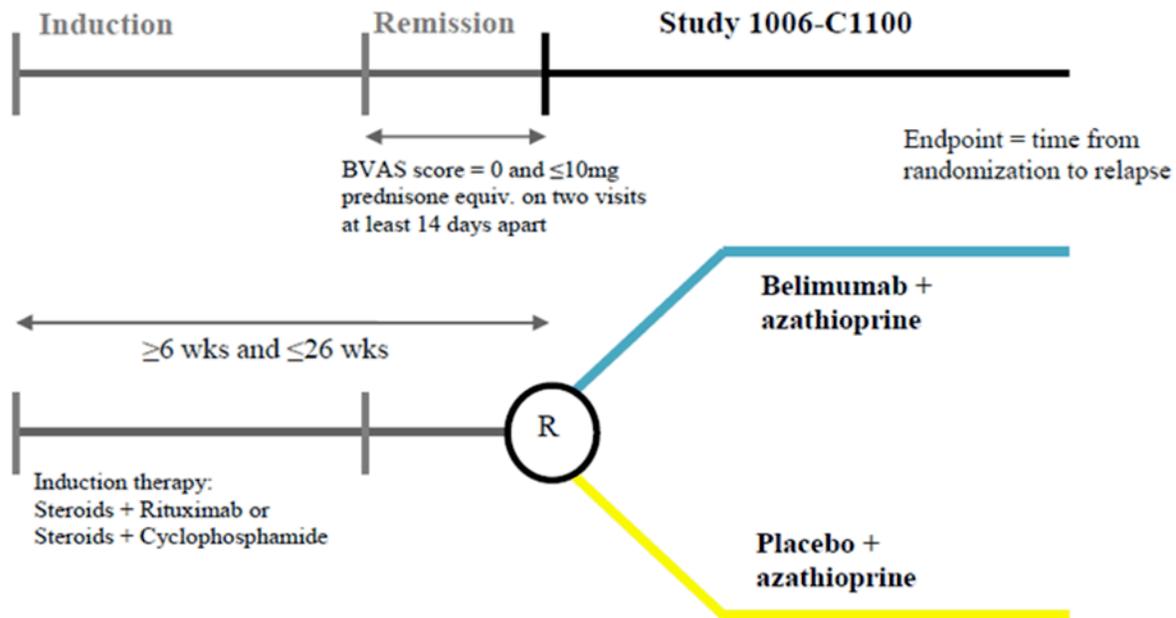
All randomized subjects should be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. Azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine should not be initiated any later than Day 0.

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Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to also receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously over 1 hour. The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). Belimumab or placebo will be supplied by the sponsor during this double-blind treatment phase. It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent will be administered at Day 0, 14, 28 and every 28 days thereafter.

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Initial randomization will be limited to 40 subjects per induction regimen (40 post-RTX induction and 40 post-CYC induction). Once the first 20 patients randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the independent data monitoring committee (DMC), who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with CYC. At all times the sites and sponsor will remain blinded to treatment allocation.

Subjects will receive study agent (belimumab/placebo) plus AZA until the study has completed or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1). The double-blind phase of the study will complete, the database will be locked, and the primary analysis will be performed when 12 months have elapsed after the last subject is randomized.

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In consultation with the investigating physician, subjects participating in the double-blind period of the trial will have the option to continue to receive treatment with belimumab in a 6-month open label extension phase. The criteria for entry into the extension phase of the study are: (1) the safety profile of belimumab is considered to be acceptable, based on ongoing IDMC data reviews of the safety data, and other relevant safety data sources; (2) the risk-benefit profile for continuing treatment with belimumab must be favorable in the opinion of the investigator; (3) the subject will have completed the double-blind treatment period of the trial without having relapsed (as defined in the primary endpoint); (4) a favorable opinion has been obtained from the local ethics committee or IRB with respect to continuation of belimumab treatment. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months and this will be supplied by the sponsor.

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Following completion of the study and, where applicable, completion of the 6-month open-label extension phase, subjects will not receive any additional treatment supplied by the sponsor. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

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Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an

attempt will be made to ascertain survival status at 12 months after the first dose of study agent.

4 Inclusion and Exclusion Criteria

4.1 Inclusion Criteria

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

1. Are at least 18 years of age.

2. Have a clinical diagnosis of Wegener's granulomatosis or a diagnosis of microscopic polyangiitis (MPA) according to the Chapel Hill criteria (Appendix 1 and Appendix 2).

3. In the 26 weeks prior to Day 0, had an episode of moderate to severely active WG or MPA requiring treatment under one of the following induction regimens:

   A single course of rituximab administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
   A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR
   cyclophosphamide 2 mg/kg/day orally plus HDCS OR
   cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

4. Have documented evidence of either anti-PR3 or anti-MPO prior to Day 0.

5. Have a Birmingham Vasculitis Activity Score (BVAS v.3 [Appendix 3]) of 0 and be receiving ≤ 10 mg/day oral prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart, between 6 and 26 weeks after the first dose of induction therapy (either CYC or RTX, as defined in Section 3.1). A minimum 6 week period should elapse between initiation of induction therapy and randomization.

6. Subjects receiving non-systemic corticosteroids for reasons other than vasculitis must be on a stable regimen prior to randomization.

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

   Not pregnant or nursing;
   Of non-childbearing potential (ie, women who had a hysterectomy, are postmenopausal which is defined as 12 consecutive months with no menses without an alternative medical cause, have both ovaries surgically removed or have current documented tubal ligation or other permanent sterilization procedure); or
   Of childbearing potential (ie, women with functional ovaries and no documented impairment of oviductal or uterine function that would cause sterility). This category includes women with oligomenorrhoea [even severe], women who are perimenopausal or have just begun to menstruate. These women must have a negative serum pregnancy test at screening, and agree to 1 of the following:
   - o Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent; or

- o Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:
  - o Implants of levonorgestrel or etonogestrel;
  - o Injectable progesterone;
  - o Transdermal contraceptive patch
  - o Any intrauterine device (IUD) with a documented failure rate of less than 1% per year;
  - o Oral contraceptives (either combined or progesterone only);
  - o Ethinyl estradiol/Etonogestrel vaginal ring;
  - o Double barrier method: Condom and Occlusive cap (diaphragm or cervical/vault caps) with spermidical foam/gel/film/cream/suppository; or
  - o 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.

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

4.2   Exclusion Criteria

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

1. Co-existence of other multisystem autoimmune diseases.

2. Known intolerance or contraindications to azathioprine (AZA); and known intolerance or contraindications to methotrexate where methotrexate is being considered as an alternative to AZA for maintenance therapy.   Amend 03 04Feb14

3. Have received treatment with a B-cell directed therapy (other than rituximab), for example anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], antiCD40L antibody [BG9588/ IDEC-131], BLyS-receptor fusion protein [BR3], LY2127399, TACI-Fc, or belimumab at any time.

4. Have required 3 or more courses of systemic corticosteroids for concomitant conditions not related to their vasculitis (eg, asthma, atopic dermatitis) within 364 days of Day 0. (Topical or inhaled steroids are permitted.)

5. Have received a non-biologic or biologic investigational agent within 60 days or 5 half-lives of the agent (whichever is the longer) of Day 0.

6. Have received a live vaccine within 30 days of Day 0.

7. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to vasculitis (ie, cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious disease) which, in the opinion of the principal investigator, could confound the results of the study or put the subject at undue risk.

8. Have a planned surgical procedure or a history of any other medical disease (eg, cardiopulmonary), laboratory abnormality, or condition (eg, poor venous access) that, in the opinion of the principal investigator, makes the subject unsuitable for the study.

9. 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.

10. Have required management of acute or chronic infections, as follows:

    Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, aspergillosis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
    Hospitalization for treatment of infection within 60 days of Day 0.
    Use of parenteral (IV, SC or IM) antibiotics, antibacterials, antivirals, anti-fungals, or anti-parasitic agents within 60 days of Day 0.

11. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 0.

12. Have a historically positive HIV test or test positive at screening for HIV.   Amend 02 25Apr13

13. Hepatitis B: Serologic evidence of Hepatitis B (HB) infection based on the results of testing for HBsAg, anti-HBc and anti-HBs as follows: Amend 02 25Apr13

    Patients positive for HBsAg are excluded.
    Patients negative for HBsAg and anti-HBc antibody but positive for anti-HBs antibody and with no history of Hepatitis B vaccination are excluded.
    Patients negative for HBsAg but positive for both anti-HBc and anti-HBs antibodies are excluded.
    Patients negative for HBsAg and anti-HBs antibody but positive for anti-HBc antibody are excluded.

14. Hepatitis C: Positive test for Hepatitis C antibody confirmed on a subsequent blood sample by RNA PCR assay. Subjects who are positive for Hepatitis C antibody and negative when the Hepatitis C RNA-PCR assay is performed on a subsequent sample will be eligible to participate. Subjects who are positive for Hepatitis C antibody and have a positive result for the HCV when the Hepatitis C RNA-PCR assay is performed on the subsequent sample will not be eligible to participate.   Amend 02 25Apr13

15. Have an IgA deficiency (IgA level < 10 mg/dL).

16. Have a Grade 3 or greater laboratory abnormality based on the protocol DMID toxicity scale, unless considered by the investigator to be related to the underlying disease or induction therapy.

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

18. Subjects who have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months and/or any suicidal ideation of type 4 or 5 on the C-SSRS (Refer to Appendix 8 for C-SSRS) in the last 2 months or who in the investigator's judgment, pose a significant suicide risk.

19. Subjects who have abnormal liver function tests defined as follows: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\geq$ 2x upper limit of normal   Amend 02 25Apr13

(ULN); alkaline phosphatase and bilirubin > 1.5xULN (isolated bilirubin > 1.5ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).

5 Study Treatment Regimen

5.1 Study Agent Name and Formulation

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

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

Belimumab drug product is provided as a sterile, lyophilized product in a 20 mL vial. Upon reconstitution with 4.8 mL sterile water for injection (SWFI), each vial will contain 80 mg/mL belimumab in 0.16 mg/mL citric acid, 2.7 mg/mL sodium citrate, 80 mg/mL sucrose, 0.4 mg/mL polysorbate 80, pH 6.5. Each vial is single use.

The placebo control is prepared as a sterile, lyophilized product in a 20 mL vial. Placebo is reconstituted with 4.8 mL SWFI. Upon reconstitution with 4.8 mL sterile water for injection (SWFI), each vial will contain 0.16 mg/mL citric acid, 2.7 mg/mL sodium citrate, 80 mg/mL sucrose, 0.4 mg/mL polysorbate 80, pH 6.5. Each placebo vial is single use.

5.2 Packaging, Labeling, Preparation, and Storage

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

Placebo control will be supplied in a 20 mL vial.

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

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

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

- Product name;
- Concentration;
- Lot number;

- Storage conditions;
- Investigational drug statement; and
- Manufacturer's name and address.

The calculated dose of study agent to be administered to the subject is determined in milligrams (mg) by the assigned treatment group and the subject's body weight in kilograms (kg).

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

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

Study agent inventory/accountability forms will be examined and reconciled by the Sponsor or designee. At the end of the study, all used and unused study agent must be accounted for on a study agent accountability form.

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

5.3   Dose, Route of Administration, and Schedule

The treatment groups include one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving azathioprine (as described in Section 5.5.3). Belimumab/placebo will be administered intravenously over 1 hour. The intent of this instruction is to prevent more rapid infusion of belimumab which may result in a higher incidence of infusion reactions. Infusion time need <u>not</u> be exactly one hour as it is often difficult to so precisely adjust infusion times and there may be clinical reasons for infusions lasting longer than one hour. Therefore, the instruction should be interpreted as infusion over <u>at least</u> one hour. The target infusion time should still be approximately one hour assuming no other issues intervene. Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days thereafter.

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

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

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase. 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. Beyond the first 2 infusions, subjects should be monitored during and for an appropriate period of time after infusion according to study sites' guidelines or standard operating procedure for IV infusions. *(Amend 04 26Feb15)*

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

5.4 Alteration of Dose/Schedule Due to Toxicity

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

If a subject experiences a clinically significant AE that the investigator believes may be definitely, possibly or probably related to belimumab/placebo and could potentially be exacerbated by the next dose, the investigator may delay the dose by up to 2 weeks or withhold 1 dose. If a similar concern is present after 2 weeks, the investigator should contact the medical monitor to determine whether treatment should be discontinued.

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

5.5   Concurrent Medications

5.5.1 Prohibited Medications and Therapies that Result in Treatment Failure

Subjects who start prohibited medication or therapies at any time during the double-blind phase will be considered as having relapsed as of the time of receipt of the prohibited medication, and treatment with study agent will be discontinued. However, the subject will continue to be followed for survival through at least 12 months after randomization. The following medications and therapies are prohibited during the study:

- Other immunomodulatory investigational agents (biologic or non-biologic);
- Rituximab;
- Cyclophosphamide;
- Other immunosuppressive agents (eg, cyclosporine) with the exception of methotrexate for AZA intolerance described in Section 5.5.3;
- Corticosteroids for vasculitis:
  doses > 20 mg/day prednisone (or equivalent), or
  IV corticosteroid pulses at any dose;
  Note: Doses of prednisone up to a maximum of 20 mg/day (or equivalent) for vasculitis, for a maximum of 1 week, are only allowable within the first 2 months of the double-blind treatment period.
- Corticosteroids for reasons other than vasculitis:
  at an average daily dose of > 20 mg/day prednisone (or equivalent) for > 14 days where the average daily dose is calculated as the sum of the dose over 7 consecutive days divided by 7, or
  IV corticosteroid pulses > 125 mg prednisone (or equivalent)
  Note: Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or IV corticosteroid pulses ≤ 125 mg prednisone (or equivalent) for reasons other than vasculitis cannot be given more than once in any 365 day period (See also Section 5.5.3).
- Plasmapharesis.

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5.5.2 Other Prohibited Medications and Therapies

Due to the mechanism of action of belimumab, it is possible that response to vaccination may be impaired. Live vaccines should not be given for 30 days before or concurrently with belimumab/placebo infusions.

Other investigational agents are not permitted.

5.5.3 Allowable Medications

The use of stable baseline dose regimens of corticosteroids (≤ 10 mg/day prednisone or equivalent) is permitted over the course of the trial. Doses of corticosteroid up to a maximum of 20 mg/day of prednisone (or equivalent), for vasculitis, are permitted for a maximum of 1 week within the first 2 months of the double-blind treatment period. At other times, subjects are restricted to ≤ 10 mg/day prednisone or equivalent. It is expected that this dose may be

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tapered as clinically appropriate. Inhaled corticosteroids for asthma, or topical corticosteroids for atopic dermatitis are also permitted. Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or an IV corticosteroid pulse up to 125 mg prednisone (or equivalent) are permitted for reasons other than vasculitis (eg. acute allergic reaction), but a subject cannot receive more than 1 such corticosteroid regimen in any 365 day period (See also Section 5.5.1).

5.5.3.1 Azathioprine and Methotrexate

The target dose of azathioprine is 2 mg/kg/day (not to exceed 200 mg/day). For the maintenance of remission azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine must not be initiated any later than Day 0. Azathioprine should be started at a dose of 50 mg/day and increased by no more than 50 mg/day every week until the target dose is achieved.
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Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. These subjects will be included in the primary analysis.
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For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset. This should be discussed with the medical monitor. Methotrexate would not be recommended for those subjects with significantly impaired renal function.
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The appropriate local prescribing information (eg, dose adjustments, contraindications, hematological and biochemical monitoring, pregnancy, contraception, etc.) for azathioprine or methotrexate (MTX) (as applicable), should be followed prior to and during treatment.

In the extension phase of the trial, the dose of AZA/MTX can be decreased or discontinued based on the discretion of the investigator.

6 Study Procedures

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

Subjects participating in the pharmacogenetics (PGx) research portion of the protocol (Appendix 9) must sign the PGx informed consent prior to any PGx samples being drawn from the subject.

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

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6.1   Screening Procedures (Day -60 to Day 0)

The following assessments are required at screening and must be within 60 days prior to or on Day 0:

- Demographics.
- Medical history.
- Lifetime cyclophosphamide exposure.
- Complete physical examination, including height, weight and vital signs.

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- Document induction regimen and confirm successful induction of remission for WG or MPA vasculitis.
- Document positive history for either anti-PR3 or anti-MPO.
- Obtain historical biopsy information for documentation of vasculitis diagnosis as available.
- Confirm subject meets study entry criteria.
- Blood samples for: (see Appendix 6 – Laboratory Tests)
  - Hematology
  - Modified Chem20 (non-fasting)
  - Serum pregnancy test – for all women with an intact uterus, unless exempted from pregnancy testing (ie, of non-childbearing potential – women who had a hysterectomy, are post-menopausal which is defined as 1 year without menses, have both ovaries surgically removed or have current documented tubal ligation or other permanent sterilization procedure)
  - HIV antibody testing, serologic investigations for Hepatitis B (HB) infection (HBsAg, anti-HBc, and anti-HBs), and Hepatitis C antibody testing ± confirmatory HCV RNA-PCR testing

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25Apr13

  - Biological markers (Complement C3, C4)
  - Serum Immunoglobulin isotypes (IgG, IgM, IgA)
  - C-reactive Protein (CRP)
  - Erythrocyte sedimentation rate (ESR)
  - Autoantibodies (ANCA: anti-PR3, anti-MPO)
- Urine Sample for:
  - Routine urinalysis
  - Spot urine for Urinary protein: urinary creatinine
- Suicidality Assessment using the Columbia Suicidality-Severity Rating Scale (C-SSRS) Screening assessment form (see Appendix 8).

6.2   Study Enrollment Procedures

Subjects who have undergone all screening procedures and have met the entry criteria will be enrolled into the study and assigned to treatment by Interactive Web Response System (IWRS). Randomization will be performed on Day 0. Azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine must not be initiated any later than Day 0. Female subjects who require pregnancy testing must have a negative urine pregnancy test done on Day 0, prior to randomization. Subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups (belimumab + AZA or placebo + AZA).

6.3   Double-Blind Treatment Phase

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

At baseline (Day 0), the subject will be randomized and receive the first dose of study agent. Visits to the study site will occur on Day 14, Day 28, and approximately every 28 days (calculated from the Day 0 dose) thereafter. All efforts should be made to retain subjects on schedule, based on the date of their Day 0 dose. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.

Subjects who have not experienced a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1) will remain on double-blind treatment with study agent until the study has completed. The double-blind phase of the study will complete and the primary efficacy analysis will be performed when 12 months have elapsed following randomization of the last subject.

In consultation with the investigating physician, subjects participating in the double-blind period of the trial will have the option to continue to receive treatment with belimumab in a 6-month open label extension phase. The criteria for entry into the extension phase of the study are: (1) the safety profile of belimumab is considered to be acceptable, based on ongoing IDMC data reviews of the safety data, and other relevant safety data sources; (2) the risk-benefit profile for continuing treatment with belimumab must be favorable in the opinion of the investigator; (3) the subject will have completed the double-blind treatment period of the trial without having relapsed (as defined in the primary endpoint); (4) a favorable opinion has been obtained from the local ethics committee or IRB with respect to continuation of belimumab treatment. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months and this will be supplied by the sponsor.

Subjects who do not enter the open-label extension will return for an Exit visit (approximately 4 weeks after the last dose of study agent), and a follow-up visit (approximately 8 weeks after the last dose of study agent).

Table 6-1 Double-blind Treatment Phase Year One

Study Visit	Screening -60 days	Day 0	Week 2 ± 3 days	Week 4 ± 3 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 16 ± 7 days	Week 20 ± 7 days	Week 24 ± 7 days	Week 28 ± 7 days	Week 32 ± 7 days	Week 36 ± 7 days	Week 40 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	Exit[11]	8 Week Follow Up[13]	Un-scheduled
Written Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eligibility Criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Document Successful Induction Regimen	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Obtain Historical Biopsy Report (if available)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Randomization	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clinical Assessments																		
Complete Physical Exam[1]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Symptom Driven Physical Exam	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Weight	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Vital Signs[15, 16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
12-lead ECG[16]	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CSSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Record Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess/Record Adverse Events[3]	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[12]	X	X
BVAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
VDI	X	X	-	-	-	X	-	-	X	-	-	X	-	-	X	X	-	-

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22Jun12

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25Apr13

Table 6-1 Double-blind Treatment Phase Year One

Study Visit	Screening -60 days	Day 0	Week 2 ± 3 days	Week 4 ± 3 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 16 ± 7 days	Week 20 ± 7 days	Week 24 ± 7 days	Week 28 ± 7 days	Week 32 ± 7 days	Week 36 ± 7 days	Week 40 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	Exit[11]	8 Week Follow Up[13]	Un-scheduled
Laboratory Assessments																		
Serum Beta hCG	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV, Hepatitis B, C[17]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology & Modified Chem-20 (non fasting)[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[14]
Coagulation – PT/aPTT and INR	X	X	-	-	X	-	-	-	X	-	-	-	-	-	X	X	-	-
Routine Urinalysis	X	-	-	-	-	X	-	-	X	-	-	X	-	-	X	X	-	-
Urine Pregnancy Test[5]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Urinary protein: urinary creatinine and creatinine clearance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X[14]
Pharmacokinetic Sampling (pre/post Belimumab dose)	-	X Pre	X Post (0-4 hrs)	-	X Pre	-	-	-	X Post (0-4 hrs)	-	-	-	-	-	X Pre	X	X	-
Pharmacogenetic Sampling[6]	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Immunogenicity (anti-belimumab antibodies)[7]	-	X	-	-	X	-	-	-	X	-	-	-	-	-	X	X	X	-
BLyS Protein	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-			-
T cells/B cell subset	-	X	-	X	X	X	-	-	X	-	-	X	-	-	X	X	X	-
C3/C4 and ANCA	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum IgG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Serum IgA & IgM	X	X	-	-	-	X	-	-	X	-	-	X	-	-	X	X	X	
CRP & ESR	X	X	-	-	-	X	-	-	X	-	-	X	-	-	X	X	X	
Protocol Treatments																		
Study agent (Belimumab/Placebo)[8, 9,]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-
AZA administration[10]	X	X	← Throughout the Study →													-	-	-

Footnotes on next page:

Amend 01 22Jun12

Amend 02 25Apr13

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Table 6-1 **Footnotes:**

1. Complete physical examination, including height and weight.

2. Any SAEs occurring prior to the start of study agent administration and assessed as related to study participation (eg, protocol-mandated procedures, invasive tests) will be recorded on the SAE worksheet and reported as described in Section 7.2 from the time a subject consents to participate in the study.

3. All adverse events (AEs) and serious adverse events (SAEs) that are identified from the start of study agent administration (Day 0) through 8 weeks following administration of the last dose of study agent should be recorded on the Adverse Event Case Report Form (AE eCRF). SAEs that occur after the 8 week follow-up period that are assessed by the investigator as definitely, possibly or probably related to study agent must be reported to the Drug Safety designee on the SAE worksheet. (Post study SAEs will not be documented on the AE eCRF.)

4. Refer to Appendix 6 for laboratory assessments to be completed.

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

6. In consenting subjects only (Appendix 9).

7. Immunogenicity samples are collected pre-dose at all time points. For any subject who had a positive antibody response at the 8-week follow-up visit (or last study visit at which immunogenicity was assessed if 8-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or after completion and/or unblinding of the study, whichever is later.

8. Subjects who discontinue treatment with study agent (belimumab/placebo) will continue to be followed per this calendar schedule until relapse as defined in Section 8.5.1.

9. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 study agent infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.

10. Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1mg/kg/day. If the patient continues to experience the toxicities described above a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset following discussion with the medical monitor.

11. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 4 weeks after the last dose of study agent). The Exit Visit should only be completed for subjects who discontinue the double blind treatment phase early or for subjects that have successfully completed the double-blind treatment phase and do not wish to participate in the open label extension phase. Subjects who discontinue treatment but have not relapsed will remain on the double blind study visit schedule. For subjects who complete the double blind phase and enter the open label phase, refer to Table 6-3 for visit details.

12. In subjects who discontinue study agent all AEs and SAEs will be reported on the AE eCRF through 8 weeks following administration of the last dose of study agent. After this time, all SAEs, regardless of relationship to study drug, will be collected until relapse or the study is analysed for the primary endpoint, whichever occurs first.

13. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent.

14. Hematology and Modified Chem 20, Urinary protein, urinary creatinine and creatinine clearance are not mandatory at Unscheduled Visits and should be obtained only when determined to be clinically indicated by the Principal Investigator.

15. Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate.

16. Complete prior to dosing.

17. HIV, Hepatitis B surface antigen, anti-HBc, anti-HBs and hepatitis C antibody (if hepatitis C antibody positive, HCV RNA-PCR assay will be performed on a subsequent blood sample to confirm the results).

Amend 02
22Apr13

Amend 03
04Feb14

Amend 04
26Feb15
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06Jul15

Amend 01
22Jun12

Amend 02
25Apr13

Table 6-2 Double-blind Treatment Phase Additional Years

Study Visit	Week 4 ± 7 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 16 ± 7 days	Week 20 ± 7 days	Week 24 ± 7 days	Week 28 ± 7 days	Week 32 ± 7 days	Week 36 ± 7 days	Week 40 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	Exit[7]	8 Week Follow Up[9]	Un-scheduled
Clinical Assessments															
Symptom Driven Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Vital Signs[11, 12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Record Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess/Record Adverse Events[1]	X	X	X	X	X	X	X	X	X	X	X	X	X[8]	X	X
BVAS	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
VDI	-	-	X	-	-	X	-	-	X	-	-	X	X	-	-
Laboratory Assessments															
Hematology & Modified Chem-20 (non fasting)[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]
Coagulation – PT/aPTT and INR	-	-	-	-	-	X	-	-	-	-	-	X	X	-	-
Routine Urinalysis	-	-	X	-	-	X	-	-	X	-	-	X	X	-	-
Urine Pregnancy Test[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Urinary protein: urinary creatinine and creatinine clearance	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X[10]
Pharmacokinetic Sampling (pre or post Belimumab dose)	-	-	-	-	-	X Pre	-	-	-	-	-	X Pre	X	X	-
Immunogenicity (anti-belimumab antibodies)[4]	-	-	-	-	-	X	-	-	-	-	-	X	X	X	-
T cells/B cells	X	-	-	-	-	X	-	-	-	-	-	X	X	X	-
C3/C4 and ANCA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Serum IgG	-	-	X	-	-	X	-	-	X	-	-	X	X	X	-
Serum IgA & IgM	-	-	X	-	-	X	-	-	-	-	-	-	X	X	-
CRP & ESR	-	-	X	-	-	X	-	-	-	-	-	-	X	X	-

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25Apr13

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22Jun12

Table 6-2   Double-blind Treatment Phase Additional Years

Study Visit	Week 4 ± 7 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 16 ± 7 days	Week 20 ± 7 days	Week 24 ± 7 days	Week 28 ± 7 days	Week 32 ± 7 days	Week 36 ± 7 days	Week 40 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	Exit[7]	8 Week Follow Up[9]	Un-scheduled
Protocol Treatments															
Study Agent (Belimumab/Placebo)[5]	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-
AZA administration[6]	X	← Throughout the Study →											-	-	-

Table 6-2 **Footnotes:**

[1] All adverse events (AEs) and serious adverse events (SAEs) that are identified from the start of study agent administration (Day 0) through 8 weeks following administration of the last dose of study agent should be recorded on the Adverse Event Case Report Form (AE eCRF).   SAEs that occur after the 8 week follow-up period that are assessed by the investigator as definitely, possibly or probably related to study agent must be reported to the Drug Safety designee on the SAE worksheet. (Post study SAEs will not be documented on the AE eCRF.)

[2] Refer to Appendix 6 for laboratory assessments to be completed.

[3] Results of urine pregnancy test at subsequent visits, if required, must be available prior to dosing. See Section 6.1 (Screening Procedures) for definition of those exempted from pregnancy testing.

[4] Immunogenicity samples are collected pre-dose at all timepoints. For any subject who had a positive antibody response at the 8-week follow-up visit (or last study visit at which immunogenicity was assessed if 8-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or after completion and/or unblinding of the study, whichever is later.

[5] Subjects who discontinue treatment with study agent (belimumab/Placebo) will continue to be followed per this calendar schedule until relapse as defined in Section 8.5.1.

[6] Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1mg/kg/day. If the patient continues to experience the toxicities described above a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted.

[7] Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 1-4 weeks after the last dose of study agent). The Exit Visit should only be completed for subjects who discontinue the double blind treatment phase early or when subjects have successfully completed the double-blind treatment phase and do not wish to participate in the open label extension phase. For subjects who complete the double blind phase and enter the open label phase, refer to Table 6-3 for visit details.

[8] In subjects who discontinue study agent all AEs and SAEs will be reported on the AE eCRF through 8 weeks following administration of the last dose of study agent. After this time, all SAEs, regardless of relationship to study drug, will be collected until relapse or the study is analysed for the primary endpoint, whichever occurs first.

[9] The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent.

[10] Hematology, Modified Chem 20, Urinary protein/urinary creatinine and creatinine clearance are not mandatory at Unscheduled Visits and should be obtained only when determined to be clinically indicated by the Principal Investigator.

[11] Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate.

[12] Complete prior to dosing.

Amend 04
26Feb15

Am01/Belgium
06Jul15

Amend 01
22Jun12

Amend 02
25Apr13

6.4   Open-Label Extension Phase

In the 6-month open-label extension, all subjects will receive 10 mg/kg belimumab every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the last dose). The first dose on the open-label extension will be given 4 weeks after completion of the double-blind period. Day 0 is the first visit in the extension phase of the trial and represents the first belimumab administration for placebo subjects. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.

All subjects participating in the open-label extension will continue to be monitored for efficacy and safety as per the study calendar (see Table 6-3).

During the 6-month open-label extension, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate. Prohibited medications during this phase are live vaccines, biological therapies and other investigational agents.

All subjects will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent. These visits apply to subjects who have completed as well as those who have withdrawn early from the open-label extension.

Following completion of the 6-month open-label extension phase, subjects will not receive any additional treatment supplied by the sponsor. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

Table 6-3   Open Label Extension Phase

Study Visit	Day 0[7]	Week 4 ± 7 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 16 ± 7 days	Week 20 ± 7 days	Week 24 ± 7 days	Week 28/ Exit[8]	8 Week Follow Up[9]	Un-scheduled
Clinical Assessments										
Symptom Driven Physical Exam	X	X	X	X	X	X	X	X	-	-
Weight	X	X	X	X	X	X	X	X	-	-
Vital Signs[11, 12]	X	X	X	X	X	X	X	X	X	-
Record Concurrent Medications	X	X	X	X	X	X	X	X	X	X
Assess/Record Adverse Events[1]	X	X	X	X	X	X	X	X	X	X
BVAS	X	-	-	-	-	-	X	X	-	-
VDI	X	-	-	-	-	-	X	X	-	-
Laboratory Assessments										
Labs: Hematology & Modified Chem-20 (non fasting)[2]	X	-	-	-	-	-	X	X	X	X[10]
Urine Pregnancy Test[3]	X	X	X	X	X	X	X	X	-	-
Urinary protein: urinary creatinine and creatinine clearance	X	-	-	-	-	-	X	X	-	X[10]
Immunogenicity (anti- belimumab antibodies)[4]	X	-	-	-	-	-	X	X	X	-
T cells/B cell subset	X	-	-	-	-	-	X	X	X	-
C3/C4 and ANCA	X	-	-	-	-	-	X	X	X	-
Serum IgG	-	-	X	-	-	-	X	X	-	-
Serum IgA & IgM	-	-	-	-	-	-	X	X	-	-
CRP & ESR	X	-	-	-	-	-	X	X	X	-
Protocol Treatments										
Study agent (belimumab)[5]	X	X	X	X	X	X	X	-	-	-
AZA administration[6]	X	← Throughout the Study →						X	-	-

Footnotes on next page:

Table 6-3 Footnotes:

[1] All adverse events (AEs) and serious adverse events (SAEs) that are identified from the start of study agent administration (Day 0) through 8 weeks following administration of the last dose of study agent should be recorded on the Adverse Event Case Report Form (AE eCRF).

[2] Refer to Appendix 6 for laboratory assessments to be completed.

[3] Results of urine pregnancy test at subsequent visits, if required, must be available prior to dosing. See Section 6.1 (Screening Procedures) for definition of those exempted from pregnancy testing.

[4] Immunogenicity samples are collected pre-dose at all timepoints. For any subject who had a positive antibody response at the 8-week follow-up visit (or last study visit at which immunogenicity was assessed if 8-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or after completion and/or unblinding of the study, whichever is later.

[5] Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.

[6] AZA/MTX continued at the discretion of the investigator.

[7] Day 0 is first visit in the extension phase of the trial and represents the first belimumab administration for placebo subjects.

[8] Any visit in which the subject discontinues treatment becomes the Exit visit (ie generally 1-4 weeks after the last dose of study agent).

[9] The 8 week follow-up visit is not required for subjects who participate in the separate continuation protocol.

[10] Hematology, Modified Chem 20, Urinary protein/urinary creatinine and creatinine clearance are not mandatory at Unscheduled Visits and should be obtained only when determined to be clinically indicated by the Principal Investigator.

[11] Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate.

[12] Complete prior to dosing.

6.5   Unscheduled Visits

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

6.6   Laboratory Tests

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

Due to the potential for unblinding, the following lab results will not be provided to study sites after baseline (Day 0): serum immunoglobulin isotypes IgM/IgA and the results from the FACS analysis listed below.

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

- T cell subsets: CD3+/CD4+, CD3+/CD8+
- B lymphocytes: (CD19+, CD20+, CD20+/CD69+ activated, CD27hi/CD20- short-lived plasma, CD27+/CD20+ memory, CD27-/CD20+ naïve, CD138+/CD20- 138 plasma cells, CD138+/CD20+ plasmacytoid, CD27−/IgD+/CD10+ transitional)

6.6.1   Pharmacokinetics

All randomized subjects who receive a dose of study agent will be sampled for the assessment of serum belimumab levels. A blood sample for pharmacokinetic analysis will be drawn according to the time schedule below.

Table 6-4   PK visit days and sample times

Week	Time (Related to Dosing of Study Agent)
0	Prior to the start of infusion
2	0-4 hours after the end of infusion
8	Prior to the start of infusion
24	0-4 hours after the end of infusion
48	Prior to the start of infusion
24 (of each additional year)	Prior to the start of infusion
48 (of each additional year)	Prior to the start of infusion
Exit visit	Any time during visit
8-week follow-up	Any time during visit

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

6.6.2   Liver Chemistry Stopping and Follow-up Criteria

Amend 02
25Apr13

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

Amend 04
26Feb15

Liver Chemistry Stopping Criteria- Liver Stopping Event	
ALT-absolute	ALT $\geq$ 8xULN
ALT Increase	ALT $\geq$ 5xULN but <8xULN persists for $\geq$2 weeks
	ALT $\geq$ 3xULN but <5xULN persists for $\geq$4 weeks
Bilirubin[1,2]	ALT $\geq$ 3xULN and bilirubin $\geq$ 2xULN (>35% direct bilirubin)
INR[2]	ALT $\geq$ 3xULN and INR>1.5, if INR measured
Cannot Monitor	ALT $\geq$ 5xULN but <8xULN and cannot be monitored weekly for $\geq$2 weeks
	ALT $\geq$ 3xULN but <5xULN and cannot be monitored weekly for $\geq$4 weeks
Symptomatic[3]	ALT $\geq$ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
1) Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT $\geq$ 3xULN **and** bilirubin $\geq$ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.	
2) All events of ALT $\geq$ 3xULN **and** bilirubin $\geq$ 2xULN (>35% direct bilirubin) or ALT $\geq$ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.	
3) New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).	

6.6.2.1   Required Actions and Follow up Assessments following ANY Liver Stopping Event

ACTIONS:

- Immediately discontinue study treatment

- Report the event to GSK **within 24 hours**

- Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE (All events of ALT $\geq$ 3xULN and bilirubin $\geq$ 2xULN (>35% direct bilirubin) or ALT $\geq$ 3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants)

- Perform liver event follow up assessments

- Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below)

Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 13).

MONITORING

For bilirubin or INR criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours**

- Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline

- A specialist or hepatology consultation is recommended

For All other criteria:
- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours**

Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline

FOLLOW UP ASSESSMENTS

- Viral hepatitis serology (includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody)

- Blood sample for pharmacokinetic (PK) analysis, obtained within approximately one to two weeks after last dose (PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Fractionate bilirubin, if total bilirubin≥2xULN

- Obtain complete blood count with differential to assess eosinophilia

- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form

- Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications

- Record alcohol use on the liver event alcohol intake case report form

For bilirubin or INR criteria:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).

- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).

Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

6.6.3   Increased Monitoring Criteria with Continued Therapy

If met see required actions below:
- If ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks OR

- ALT ≥3xULN **and** <5xULN and bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks

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

- Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety.

- Subject can continue study treatment

- Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline

- If at any time subject meets the liver chemistry stopping criteria, proceed as described above for Required Actions and Follow up Assessments following ANY Liver Stopping Event

- If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly.

- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

6.6.4 Study Treatment Restart

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

Approval by GSK for study treatment restart can be considered where:
- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).

- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an HLA genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.

- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.

- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.

- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.

- Study treatment must be administered at the dose specified by GSK.

- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.

- GSK to be notified of any adverse events, as per Section 7.2

6.6.5 Immunogenicity

Serum samples for the measurement of anti-belimumab antibodies will be obtained from all subjects before administration of study agent on Day 0, Week 8, Week 24, Week 48 and Exit/8-week Follow-up. Additionally, samples will be obtained from subjects at Weeks 24 and 48 during additional years. For any subject who had a positive antibody response at the 8-week follow-up visit (or last study visit at which immunogenicity was assessed if 8-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or after completion and/or unblinding of the study, whichever is later.

6.7   Exit Visit

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

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an attempt will be made to ascertain survival status at 12 months after the first dose of study agent.

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

6.8   8-Week Follow-up Visit

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

Refer to the Study Calendar (see Table 6-1, Table 6-2 and Table 6-3) for a list of procedures required at this visit.

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6.9   Withdrawal of Subjects from Treatment

Subjects will be free to withdraw from treatment or from the study at any time, for any reason, or they may be withdrawn/removed, if necessary, to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

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

- Unacceptable toxicity (see Section 5.4)
- Prohibited concurrent medication or therapy (see Section 5.5.1 and Section 5.5.2)
- Withdrawal of consent (including use and disclosure of research-related health information)
- Pregnancy

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an attempt will be made to ascertain survival status 12 months after the first dose of study agent. Any subject that withdraws consent for use and disclosure of research-related health information will be considered withdrawn from the study and not followed.

6.10   Subject Unblinding

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

If a medical emergency occurs and a decision regarding the subject's condition requires knowledge of the treatment assignment, the study blind may be broken for the specific subject. Whenever possible, the investigator should consult with the medical monitor prior to unblinding any subject. Any broken blind will be clearly justified and explained by a comment in the eCRF. The investigator must notify the Medical Monitor of any broken blind, regardless of whether it was done for emergency or non-emergency reasons.

7 Adverse Event Reporting

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

7.1   Definitions

ADVERSE EVENT

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

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

Events meeting the definition of an AE include:

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

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

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

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

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

a. Results in death

b. Is life-threatening

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

c. Requires hospitalization or prolongation of an existing hospitalization

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

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

d. Results in disability / incapacity, or

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

e. Is a congenital anomaly / birth defect

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

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

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

7.2 Reporting Adverse Events to the Sponsor

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

For subjects who discontinue treatment with study agent during the double-blind period (for reasons other than withdrawal of consent), all adverse events will be collected through 8 weeks following the administration of the last dose of study agent. After this time, all SAEs, regardless of relationship to study drug, will be collected until relapse or the study is analysed for the primary endpoint and study sites are informed that SAE data collection can cease, whichever occurs first.

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

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

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

7.3 Other Events Requiring Rapid Reporting (Protocol Specified Events)

Protocol Specified Events (PSEs) are additional events that must be reported to the Drug Safety designee in an expedited manner. A PSE may or may not be an SAE. PSEs are considered SAEs if they meet 1 or more of the criteria for an SAE (See Section 7.1). PSEs are

recorded on the PSE page of the eCRF within 24 hours of site personnel becoming aware of the event.

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

7.4   Laboratory Abnormalities as Adverse Events

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

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

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

7.5   Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. A diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The subject should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping all immunosuppressant therapy.

If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

7.6   Suicidality Assessment

Some autoimmune diseases have an increased risk of suicidal behavior and/or ideation (Bachen et al, 2009, Timonen et al, 2003, Stenager et al, 1992). In order to objectively assess suicidality in belimumab clinical programs the C-SSRS will be utilized to collect information on suicidal behavior and ideation. Since major depressive disorder may increase the risk of suicidal ideation or behavior before or during clinical studies, subjects participating in this study will be assessed at every visit for suicidality.

Subjects who answer "yes" to any suicidal behavior or "yes" to suicidal ideation questions 4 or 5 on the C-SSRS should be referred to appropriate psychiatric care and prompts the completion of an SAE worksheet. The medical monitor should be notified when these events occur. In addition, a "yes" to any suicidal behavior or "yes" to suicidal ideation question 3, 4 or 5 on the C-SSRS prompts the completion of the Possible Suicidality Related History Questionnaire (PSRHQ, only the first time this condition is met; refer to Appendix 10 for the PSRHQ) eCRF and a Possible Suicidality Related Questionnaire (PSRQ) eCRF (at all times this condition is met; refer to Appendix 11 for the PSRQ).

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

Amend 02
25Apr13

Although assessment of suicidality using the C-SSRS will take place only during the blinded portion of the study, investigators are reminded of the importance to clinically assess for suicidality at every visit given that study patients are at increased risk of suicidal behavior and/or ideation.

7.6.1 Possible Suicidality Related Questionnaire (PSRQ)

The investigator will be prompted to complete the PSRQ (in addition to the AE or SAE pages, as appropriate) if a yes response is given to any suicidal behavior or a yes response to suicidal ideation questions 3, 4 or 5 on the C-SSRS. Refer to Appendix 11 for the PSRQ. If the adverse event meets the definition of an SAE, which includes a yes answer to any suicidal behavior or a yes to suicidal ideation questions 4 or 5 on the C-SSRS the site must ensure that there are no significant discrepancies between the PSRQ and the SAE.

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7.7 Reporting a Pregnancy

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Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to the Sponsor within 2 weeks of learning of its occurrence. All pregnancies that are identified from the start of study agent through 16 weeks following the last dose of study agent should be reported. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

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

7.8   Investigator Evaluation of Adverse Events

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

SEVERITY

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

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

CAUSALITY

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.9   Follow-Up of Adverse Events

Serious and non-serious adverse events that occur from the start of study medication administration through 8 weeks after the date of last administration of study agent are reported.

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

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

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

All SAEs that are considered by the sponsor to be unexpected and related to belimumab will be reported by the sponsor or designee as expedited (eg, 15-Day) reports to the appropriate regulatory authorities AND to all participating investigators (exceptions discussed below). In addition, the sponsor or designee follows all applicable local and national regulatory requirements regarding safety reporting. Each investigator must also comply with the applicable regulatory requirements related to the reporting of SAEs to the IRBs/IECs responsible for reviewing the study at their site, as well as the regulatory authority(ies) (if applicable).

All serious adverse events, including serious disease-related events (discussed below), will be monitored by treatment group by an independent DMC. Investigators and IRBs/IECs will be notified of the outcome of each DMC meeting, and any recommendations made.

The conditions listed in Appendix 3 are disease related events that can occur in the study population regardless of belimumab exposure. When these conditions are considered SAEs, they must be reported to the Sponsor within 24 hours of site personnel becoming aware as described in Section 7.2. Where these are clearly related to the underlying vasculitis, the Sponsor may not submit them as expedited reports to regulatory authorities or participating investigators.

8 Endpoints and Statistical Analysis

8.1   General Statistical Considerations

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

The database will be locked for the primary analysis after all data have been collected, verified and validated for all subjects through 12 months after the randomization of the last subject. All subjects and study site personnel will remain blinded to original treatment assignment until after the final database is locked and the results of the study are made publicly available. Amend 04 26Feb15

Analysis of primary and secondary endpoints will be exploratory in nature. Nominal p values may be reported and considered descriptive. Where appropriate point estimates and 95% confidence intervals will be constructed.

8.2   Randomization Procedure and Assignment to Treatment Groups

This is a multi-center, multinational, randomized, double-blind, placebo-controlled study. Amend 04 26Feb15 Once subjects have consented, have undergone all screening procedures and have been determined to be eligible for the study, they will be randomly assigned (via an interactive web response system [IWRS]) to 1 of 2 treatment groups (belimumab [10 mg/kg] or placebo) in a 1:1 ratio. At randomization, subjects will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. RTX). Randomization will be performed on Day 0.

8.3   Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will review safety data on an ongoing basis until the data are locked and analyzed (after which monitoring may be assumed by an internal HGS committee). The DMC will include at least 3 physicians and a statistician, none of whom are affiliated with the Sponsor. Initial randomization will be limited to 40 subjects per induction regimen (40 post-RTX induction and 40 post-CYC induction). The first DMC reviews will occur after the first 20 subjects per induction regimen (RTX or IV/oral CYC) have been randomized and have had a Week 8 visit. Once the first 20 subjects randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the DMC, who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with CYC. The DMC will review the data approximately every 6 months thereafter across both induction regimens. At all times the sites and sponsor will remain blinded to treatment allocation. Investigators and IRBs/IECs will be notified of the outcome of each DMC meeting.

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The DMC will receive information within 72 hours of the sponsor or designee receiving notification of any IgG < 250 mg/dL and all unexpected causally-related SAEs that are life threatening or result in death. Other unexpected, causally-related SAEs will be provided to the DMC within 15 calendar days. In addition, the DMC will receive information on all serious infections and all opportunistic infections, irrespective of relationship to study agent, within 15 calendar days.

8.4 Sample Size Rationale

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Approximately 100 subjects will be randomized. The sample size has been determined based on the feasibility of enrolling patients into the study within a reasonable time-frame. The sample size was not based on statistical considerations and the analysis of primary and secondary endpoints will be exploratory in nature. The primary efficacy analysis will be performed after 12 months have elapsed following randomization of the last subject.

Although the sample size is based on feasibility, the minimal detectable effect has been determined. Assuming an observed relapse rate at 18 months of 20% in the placebo group, a relapse rate of ≤7.0% on belimumab (hazard ratio ≤0.32) would be statistically significant (p<0.05) in a study of 100 subjects (50 per arm).

8.5 Efficacy

8.5.1 Primary Efficacy Endpoint

The primary endpoint is time from Day 0 to the first relapse, defined as

- at least 1 major BVAS item (Appendix 4) OR
- a minimum total BVAS score of 6 (Appendix 4) OR
- receipt of prohibited medications (as defined in Section 5.5.1).

8.5.2 Primary Efficacy Analysis

The primary efficacy analysis will compare the time to first relapse from Day 0 between the placebo/azathioprine group and the belimumab/azathioprine combination group using a Cox proportional hazard model, adjusted for ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide). However, the adjustment of induction regimen will be changed to rituximab vs. IV and/or oral cyclophosphamide if the number of events (relapse) is less than 5 in subjects using the oral or IV cyclophosphamide. If there are then still less than 5 patients with an event (relapse) in any of the levels of this or any other stratification factor then the stratification term may be removed from the model. For any subject who does not experience a relapse, the time to first relapse will be censored at the time of the subject's last assessment. Subjects who discontinue study agent prior to relapse/flare (as defined in primary efficacy endpoint) are to be followed per protocol for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The database will be locked and the primary efficacy analysis will be performed after 12 months have elapsed following randomization of the last subject.

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8.5.3 Major Secondary Efficacy Endpoint

1. Time from Day 0 to the first major relapse (defined as experiencing at least 1 major BVAS item).

8.5.4 Other Efficacy Endpoints

1. Time from Day 0 to first minor or major relapse (defined as experiencing at least 1 minor BVAS item and/or using a dose of rescue medication).
2. Absolute change in Vasculitis Damage Index (VDI) at double-blind Week 48 of Year 1 and double-blind Week 28 of Year 2 and by visit;
3. Proportion of subjects with any increase in VDI at double-blind Week 48 of Year 1 and double-blind Week 28 of Year 2 and by visit;
4. Absolute change in BVAS at double-blind Week 48 of Year 1 and double-blind Week 28 of Year 2 and by visit;
5. Proportion of subjects with any increase in BVAS at double-blind Week 48 of Year 1 and double-blind Week 28 of Year 2 and by visit; and
6. Proportion of subjects with any increase in BVAS organ domains at double-blind Week 48 of Year 1 and double-blind Week 28 of Year 2 and by visit and by domain.
7. Proportion of patients in remission (defined as BVAS=0 and corticosteroid dose < 10 mg/day) at double-blind Week 48 of Year 1, double-blind Week 28 of Year 2 and by visit.
8. Proportion of patients with no relapse at double-blind Week 48 of Year 1, double-blind Week 28 of Year 2 and by visit.

Biological Markers and Autoantibodies:

Pharmacogenetic sampling (in consenting subjects) will be taken once during the course of this study (see Appendix 9).

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

- Anti-neutrophil cytoplasmic antibody (ANCA – anti-PR3, anti-MPO)
- Serum complement (C3, C4)
- Serum immunoglobulin isotypes (IgA, IgM, IgG)
- C-reactive Protein (CRP)
- Erythrocyte sedimentation rate (ESR)
- Urinary protein: urinary creatinine ratio
- BLyS protein (Day 0 only)

- FACS of peripheral lymphocytes:
  B lymphocytes (CD19+, CD20+, CD20+/CD69+ activated, CD27hi/CD20- short-lived plasma, CD27+/CD20+ memory, CD27-/CD20+ naïve, CD138+/CD20- 138 plasma cells, CD138+/CD20+ plasmacytoid, CD27−/IgD+/CD10+ transitional)
  T cell subsets: CD3+/CD4+, CD3+/CD8+

8.5.5 Major Secondary Endpoint analysis and Other Efficacy Analyses

The exploratory analysis of the major secondary efficacy endpoint will be performed using the same method described for the primary efficacy endpoint, but censoring subjects who receive any prohibited medication (as defined in Section 5.5.1) prior to an observation of any major BVAS item. Any censoring will be applied on the date prohibited medications are received. Amend 04 26Feb15

The analysis of other efficacy endpoints, biomarkers, and auto-antibodies measurements will be described in the statistical analysis plan.

8.6   Safety

8.6.1 Definition of Safety Variables

Safety will be evaluated by adverse events, changes in laboratory parameters, suicidality assessment (Appendix 8), and immunogenicity.

8.6.2 Analysis of Safety Variables

AEs will be graded for severity by the investigator using Adverse Event Severity Grading Tables (Appendix 7) or as described in Section 7.8, as appropriate. The frequency and rate of AEs will be tabulated by MedDRA system organ class (SOC) and preferred term. Additional analyses may be performed based on event rates adjusting for subject-years on study agent if the time on study agent is imbalanced across treatment groups. Serious and severe (Grade 3 and Grade 4) AEs will also be summarized by MedDRA SOC and preferred term. Discontinuations due to AEs will be summarized.

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

Safety Endpoints of Special Interest

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

- Infusion reactions including hypersensitivity reactions
- Immunogenicity

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

8.7 Pharmacokinetics

8.7.1 Definition of Pharmacokinetic Evaluation

All randomized subjects who receive a dose of study agent will be sampled for the assessment of serum belimumab levels. Assessment of belimumab concentrations will be performed at the timepoints indicated in Section 6.6.1.

8.7.2 Analysis of Pharmacokinetics

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

9 Pharmacogenetics (PGx)

In consenting subjects, a blood sample for PGx research will be drawn at baseline (Day 0) to better characterize genetic variability (eg, HLA typing) that may affect efficacy or safety endpoints. Information regarding PGx research is included in Appendix 9.

The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the study site. The approval(s) must be in writing and clearly specify approval of the PGx assessments (ie, approval of Appendix 9). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate that approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments are not approved, then approval for the rest of the study will clearly indicate this and that PGx assessments will not be conducted.

10 Study Administration

Belimumab is under joint development by Human Genome Sciences, Inc and GlaxoSmithKline Pharmaceuticals. Human Genome Sciences, Inc. is the sponsor of the study.

10.1 Informed Consent

A copy of the proposed informed consent document must be submitted to the Sponsor or designee for review and comment prior to submission to the reviewing IRB/IEC. The consent

form must be approved by the IRB/IEC and contain all elements required by national, state, local, and institutional regulations or requirements.

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

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

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

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

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

10.3 Protocol Compliance

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

10.4 Protocol Revisions

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

10.5 Data Collection and Management

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

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

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

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

10.6 Study Monitoring

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

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

10.7 Drug Accountability

Upon receipt, the investigator is responsible for taking an inventory of the study agent, including any buffers or diluents. A record of this inventory must be kept and usage must be documented on study agent inventory forms provided by the Sponsor.

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

10.8 Retention of Records

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

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

10.9 Financial Disclosure

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

10.10 Publication Policy

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

The investigator shall submit a copy of any proposed publication, manuscript, abstract, presentation or other document with respect to this study to the Sponsor for review and comment at least 60 days prior to its submission for publication or presentation. No publication or presentation with respect to the study shall be made unless and until all of the

Sponsor's comments on the proposed publication or presentation have been considered and any information determined by Sponsor to be confidential information has been removed. If requested in writing by the Sponsor, the investigator shall withhold material from submission for publication or presentation for an additional 60 days to allow for the filing of a patent application or the taking of other measures to establish and preserve the Sponsor's proprietary rights.

10.11 Study or Study Site Termination

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

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of HGS to suspend or discontinue testing, evaluation, or development of the product for WG or MPA.

The study site may warrant termination under the following conditions:

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

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List of Appendices

Appendix 1   Chapel Hill Consensus Definition for Granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) (Jennette et al, 2013)

Amend 02
25Apr13

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The CHCC Definition requires:

Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium-sized vessels (eg, capillaries, venules, arterioles, and arteries) for a diagnosis of Wegener's.

Another feature that may be commonly present in GPA, but which is not required according to the CHCC definition, is necrotizing glomerulonephritis.

Appendix 2   Chapel Hill Consensus Definition for Microscopic Polyangiitis (MPA) (Jennette et al, 2013)

Amend 02
25Apr13

Amend 03
04Feb14

The CHCC definition requires:

Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (ie, capillaries, venules, or arterioles) for a diagnosis of MPA. Granulomatous inflammation is absent.

Other features that may be present in MPA, but that are not required according to the CHCC definition, are: necrotizing arteritis involving small- and medium-sized arteries; commonly necrotizing glomerulonephritis; and often pulmonary capillaritis.

Appendix 3   BVAS Activity Assessment Form

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

Appendix 4   BVAS Item Scoring

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

Appendix 5   Vasculitis Damage Index

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

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VASCULITIS DAMAGE INDEX (VDI)
INVESTIGATOR INSTRUCTIONS

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Protocol Identifier	Subject Identifier	Date of Assessment			Visit Description ✓ one:		
		Day	Month	Year	☐ Screening ☐ Day 0	☐ Year___ ☐ Week 12 ☐ Week 24 ☐ Week 36 ☐ Week 48 ☐ Exit	☐ OL Day 0 ☐ OL Week 24 ☐ OL Week 28/Exit
BEL115466							

VASCULITIS DAMAGE INDEX (VDI)

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Appendix 6 Laboratory Tests[1]

Hematology
Total white blood cell count
Differential:
 Absolute Neutrophils
  Segmented Neutrophils
  Band Neutrophils
  Myelocytes
  Metamylocytes
  Promyelocytes
 Lymphocytes
 Monocytes
 Eosinophils
 Basophils
Hemoglobin
Hematocrit
Red blood cell (RBC) count
Platelet count
Prothrombin time (PT)
Partial thromboplastin time (PTT)
INR
Serum Pregnancy

Biological Markers

FACS of peripheral lymphocytes:
T cell subsets: CD3+/CD4+, CD3+/CD8+
B lymphocytes (CD19+, CD20+, CD20+/CD69+ activated, CD27hi/CD20- short-lived plasma, CD27+/CD20+ memory, CD27-/CD20+ naïve, CD138+/CD20- 138 plasma cells, CD138+/CD20+ plasmacytoid, CD27−/IgD+/CD10+ transitional)

BLyS protein
Serum complement (C3 and C4)
C-Reactive Protein (CRP)
Erythrocyte sedimentation rate (ESR)

Immunoglobulins
Serum immunoglobulin isotypes: IgG, IgM, IgA

PK and Immunogenicity

Autoantibodies
ANCA (anti-PR3; anti-MPO)

Urinalysis
Protein
Glucose
Ketones
Occult blood
Microscopic examination including:
 WBC per hpf
 RBC per hpf
 Casts (specified by type eg, RBC, WBC)
Spot Urine (protein : creatinine ratio)
Urine Pregnancy

Modified Chem-20
Electrolytes:
 Sodium
 Potassium
 Magnesium
 Chloride
 Carbon dioxide
 Calcium adjusted for Albumin
 Inorganic Phosphate Amend 01 22Jun12
Enzymes:
 SGOT (AST)
 SGPT (ALT)
 Alkaline Phosphatase
 Gamma glutamyl transferase (GGT)
 Lactate dehydrogenase (LDH)
Other:
 Creatinine
 Blood urea nitrogen (BUN)
 BUN/creatinine ratio
 Bilirubin, total
 Protein, total
 Albumin
 Uric acid
 Glucose
 HIV-1/2 antibody Amend 02 25Apr13
 Hepatitis C antibody (± HCV RNA PCR for confirmation of positive antibody test)
 Hepatitis B surface antigen
Hepatitis B surface and core antigen antibodies Amend 02 25Apr13
Estimated Creatinine Clearance/ GFR (Cockcroft-Gault)

Liver event follow-up assessments: Amend 02 25Apr13
Hepatitis A IgM antibody
HBsAg and HB Core antibody (IgM)
Hepatitis C RNA
Cytomegalovirus IgM antibody
Epstein-Barr viral capsid antigen IgM antibody
Hepatitis E IgM antibody
CPK
Anti-smooth muscle antibody
Type 1 anti-liver kidney microsomal antibodies Amend 02 25Apr13

[1]Institution or country specific guidelines for blood sample volume limits must be followed in collection of the subsequent blood sample.

Appendix 7   Adverse Event Severity Grading Tables

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

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

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

Modified from DMID Adult Toxicity Tables, 2001

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

(continued)

Modified from DMID Adult Toxicity Tables, 2001

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

*(Goldfarb et al, 2001; Yamani et al, 2001; Eibl and Rosen, 1995).   Modified from DMID Adult Toxicity Tables, 2001

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

Modified from DMID Adult Toxicity Tables, 2001

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

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

RBC = red blood cell; hpf = high power field.   Modified from DMID Adult Toxicity Tables, 2001

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

Modified from DMID Adult Toxicity Tables, 2001

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

Modified from DMID Adult Toxicity Tables, 2001

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

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

COLUMBIA SUICIDE-SEVERITY RATING SCALE (C-SSRS)
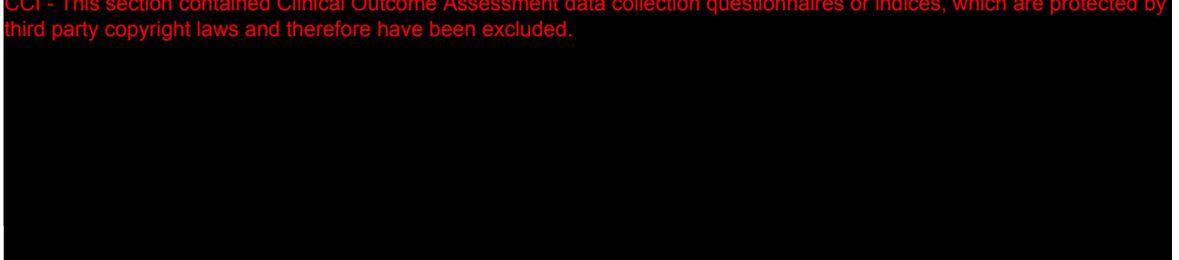
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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Appendix 9   Pharmacogenetic Research

Background

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

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

Research Rationale

Systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies but little is known regarding the genetic contribution to risk for developing different forms of vasculitis. Recent gene studies in vasculitis are identifying both common polymorphisms associated with other autoimmune but also completely different associations (Monach and Merkel, 2010).

Amend 02
25Apr13

There is growing evidence for a genetic contribution to the risk of developing different forms of vasculitis (Monach and Merkel, 2010) for example the association of alpha 1-antitrypsin deficiency in WG.

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Blood samples for pharmacogenetics will be drawn as described in Section 9. Insights into the genetic pathways underlying AAV may help identify subgroups of patients that may have additional benefit from therapies from specific therapies. Fc Receptor polymorphism analysis may further define the interaction between underlying genetic heterogeneity and the therapeutic endpoints utilized in this trial.

Collection of whole blood samples may enable PGx analyses to be conducted if there are any unexplained or unexpected results.

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

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

Study Population

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

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

Informed Consent

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

Study Assessments and Procedures

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

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

The need to conduct PGx analysis may be identified after a study (or set of studies) of belimumab has been completed and the study data reviewed. In some cases, the samples may not be studied ie, no questions are raised about how people respond to belimumab.

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

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

Subject Withdrawal from Study

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

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

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

Screen and Baseline Failures

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

Pharmacogenetics Analyses

Specific sections of DNA may be selected from areas of the genome (ie, candidate genes) known to encode the drug target, drug metabolizing enzymes, areas associated with mechanisms underlying adverse events, and those linked to study disease and, thus, linked to drug response.

Generally, two approaches will be utilized to explore genetic variation in drug response.

The candidate genes that may be selected and investigated in this study are the following:

- HLA alleles
- Alpha-1 anti-trypsin (A1AT)
- Fc receptors
- Cytokines, immune receptors and chemokines related to immune cell function

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

By evaluating large numbers of polymorphic markers (eg, single nucleotide polymorphisms or SNPs) throughout the genome, sets of markers may be identified that correspond to differential drug response. These will include:

- **Hardy-Weinberg Equilibrium Testing**

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

- **Comparison of Demographic and Baseline Characteristics by Genotype**

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

- **Evaluation of Genotypic Effects**

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

- **Evaluation of Treatment by Genotype and Gene-Gene Interaction**

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

- **Linkage Disequilibrium**

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

- **Multiple Comparisons and Multiplicity**

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

- **Power and Sample Size Considerations**

  The ability to detect differential drug response among genotypes at a polymorphic site depends on the total number of subjects genotyped and the frequency distribution of the different genotypes. Consequently, genotyping analyses are plausible for those polymorphic sites where the number of subjects comprising the genotypic groups is sufficiently large; however, these frequencies will not be known until sufficient samples have been collected and genotyping is complete.

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

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

Appendix 10   Possible Suicidality Related History Questionnaire (PSRHQ)

Amend 02
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gsk GlaxoSmithKline | **Protocol Identifier** | **BEL115466** | Final - 16 JAN 13

POSSIBLE SUICIDALITY-RELATED HISTORY QUESTIONNAIRE (PSRHQ) INSTRUCTIONS

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

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

And/or

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

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

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

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

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Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
BEL115466			_____

Date of assessment | [ ][ ] Day | [ ][ ] Month | [ ][ ] Year |

POSSIBLE SUICIDALITY-RELATED HISTORY QUESTIONNAIRE

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

[Y] ☐ Yes   [N] ☐ No

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

	Event	Date (DDMMMYYYY)
☐	Cerebrovascular Accident	
☐	Headache	
☐	Meningitis	
☐	Organic Confusion	
☐	Seizures	

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

Appendix 11   Possible Suicidality Related Questionnaire (PSRQ)

Amend 02
25Apr13

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gsk GlaxoSmithKline	**Protocol Identifier**	**BEL115466**

Final - 15 JAN 13

POSSIBLE SUICIDALITY-RELATED QUESTIONNAIRE (PSRQ)
INSTRUCTIONS

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

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

And/or

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

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

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

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

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

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

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

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

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

gsk GlaxoSmithKline   CONFIDENTIAL   Final - 15 JAN 13

Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
BEL115466			_____

Date of assessment [ ][ ] [ ][ ] [ ][ ]
Day   Month   Year

POSSIBLE SUICIDALITY-RELATED QUESTIONNAIRE (PSRQ)

☐ Not Done

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

If Yes, check all that apply:

☐ Amphetamines   ☐ Benzodiazepines   ☐ Cannabinoids   ☐ Cocaine   ☐ Opiates

☐ Other, Specify: _____

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

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

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

If Yes, check all that apply:

☐ Family Problems   ☐ Relationships   ☐ Employment/ Unemployment   ☐ Finances

☐ Other Factors, Specify:_____

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

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

Father   ☐ Ideation   ☐ Behavior

Mother   ☐ Ideation   ☐ Behavior

Sibling   ☐ Ideation   ☐ Behavior

Other   ☐ Ideation   ☐ Behavior

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

If Yes, specify disorder next to all that apply:

Father   _____

Mother   _____

Sibling   _____

Other   _____

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

Appendix 12   Protocol Addendum – Benefit and Risk Assessment

Disease Background

Amend 02
25Apr13

The systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies including infective and drug-induced causes and can be either primary or secondary to other diseases such as SLE. A subset of the primary small vessel vasculitides: Wegener's granulomatosis; also known as granulomatosis with polyangiitis (GPA), microscopic polyangiitis and Churg-Strauss syndrome (CSS), are characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) (Jennette and Falk, 1997). ANCA-associated vasculitides (AAV) are multisystem diseases with a broad range of manifestations from cutaneous ulcers, scleritis, pericarditis to lifethreatening manifestations such as lung hemorrhage and renal failure. All 3 forms of AAV share the characteristic of systemic necrotizing vasculitis; WG and CSS are further characterized by granuloma formation.

Historically, ANCA have been classified on the basis of their staining patterns in immunofluoresence assays as either cytoplasmic (C-ANCA) or perinuclear (P-ANCA). It is now recognized that in AAV, C-ANCA is usually directed against proteinase 3 (PR3), and P-ANCA is generally directed against myeloperoxidase (MPO), both of which are enzymes that are abundant in the granules of neutrophils (Jennette and Falk, 1997; Merkel et al, 1997). Anti-PR3 antibodies are generally associated with WG, while anti-MPO autoantibodies are more common in MPA and CSS. Anti-PR3 antibodies are associated with increased morbidity and mortality compared to anti-MPO. The most widely used classification criteria for diagnosing the 3 types of AAV are those published by the American College of Rheumatology (ACR) for WG and CSS (Leavitt et al, 1990 and Masi et al, 1990, respectively), and that published by the Chapel Hill Consensus Conference (CHCC) for MPA (Jennette et al, 1994). Of note, none of these diagnostic criteria incorporate the measurement of ANCA.

The precise epidemiology of these diseases is uncertain as early studies did not utilize the same classification criteria as later ones (Koldingsnes and Nossent, 2008; Watts et al, 2007). In the case of MPA, in particular, epidemiological studies are confounded by its original inclusion as a form of polyarteritis nodosa (PAN). Utilizing the ACR or CHCC criteria, prevalence rates range from 5-16/100000 for WG, 2.5-9.4/100000 for MPA, and 0.4-1.4/100000 for CSS making the latter the least prevalent of the three by some margin (Koldingsnes et al, 2008). AAV are extremely rare in childhood with peak age of onset in those aged 65 to 74 years (Ntatsaki et al, 2010), with other small vessel vasculitides being the major concern in childhood (Brogan et al, 2010).Current therapy is usually determined by severity of the disease, with more severe forms warranting more aggressive approaches. These usually involve an initial remission induction regimen of high dose corticosteroid administered with either cyclophosphamide (CYC) or rituximab (RTX) followed by a remission maintenance period usually with azathioprine (Stone et al, 2010; Bosch et al, 2007; Jayne et al, 2003). Minor manifestations are usually treated with low dose corticosteroid administered with either azathioprine or methotrexate (Belmont, 2006). Even with recent

treatment advances the morbidity and mortality of patients with AAV remains unacceptably high (Drooger et al, 2009).

The Birmingham Vasculitis Activity Score (BVAS) was developed and validated as a tool to measure disease activity (Luqmani et al, 1994). It has been modified to form the BVAS/WG (Stone et al, 2001) and updated most recently with the validation of version 3 of the instrument, also known as BVAS 2003 (Mukhtyar et al, 2009). In its current form it is a list of 56 items which are considered to be manifestations of vasculitis. A weighted numerical score is attached to each item to reflect the importance of each manifestation. The items are grouped by organ systems, and each organ system has a maximum or 'ceiling' score to reflect the relative importance of the organ system (Mukhtyar et al, 2009). The tool also makes a distinction between new or worsening disease and persistent disease with new or worsening attracting higher scores.

IV Belimumab

Over 2,000 individuals with SLE have been treated with belimumab in clinical studies. In two global Phase 3 studies, belimumab 10 mg/kg met the primary efficacy endpoint (SRI at Week 52). Evidence of other possible benefits in these trials included reductions in risk of severe flare and corticosteroid use, and improvements in patient reported quality of life and fatigue. Serological activity was reduced as measured by reductions in autoantibodies and normalization of hypergammaglobulinemia and complement levels. B cells, including autoreactive B cells, were also reduced, but not severely depleted, consistent with what would be expected from inhibition of BLyS (reference belimumab IB, Section 5.3.1). These results supported the approval of belimumab in the EU, US, Canada and other countries.

In the United States belimumab is approved for the following indication:

> *BENLYSTA® (belimumab) is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.*

> *Limitations of Use: The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of BENLYSTA is not recommended in these situations.*

In the EU, the approved indication focuses on patients with high disease activity (where belimumab offered the greatest benefit):

> *Benlysta is indicated as add-on therapy in adult patients with active, autoantibodypositive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g positive anti-dsDNA and low complement) despite standard therapy.*

The EU SPC also includes special warnings and precautions for use similar to the US labeling, including that belimumab has not been studied in and is thus not recommended in

patients with severe active central nervous system lupus or severe active lupus nephritis. In addition, caution should be exercised if belimumab is co-administered with other B cell targeted therapy or cyclophosphamide. Reference Section 4.4 of the SPC for the complete list of specials warnings and precautions.

Treatment with belimumab plus standard therapy was generally well tolerated, with rates of AEs, severe AEs, SAEs, AEs leading to discontinuation, and serious/severe infections generally comparable to the rates observed in the placebo plus standard therapy group. The most commonly-reported adverse reactions, occurring in $\geq 3\%$ of patients receiving 10 mg/kg belimumab IV in clinical trials (and at a $\geq 1\%$ greater rate than placebo) were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, cystitis, leukopenia, and gastroenteritis viral. In clinical trials, hypersensitivity and infusion reactions were observed more frequently with belimumab, with anaphylaxis observed in $\leq 1\%$ of subjects. Data from the post-marketing setting indicate that hypersensitivity reactions may be serious or result in death, that the onset of such reactions may be delayed, and that patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. In addition, it is also known from clinical trials and the post-marketing setting that the vast majority of hypersensitivity reactions occur with the 1st or 2nd infusion. The product labeling, belimumab IB, protocol, and informed consent forms have been updated to include this new information, as applicable.

Other risks that may be associated with belimumab based on its mechanism of action include serious infections and malignancy, although no increases in the rates of serious infections or malignancies have been observed. Psychiatric events including depression and suicide were observed more frequently with belimumab than with placebo, although it is unknown if belimumab treatment is associated with an increased risk for these events. Finally, mortality rates in the controlled clinical trials were low, although numerically higher in the belimumab groups (0.4% and 0.8% in the placebo and belimumab groups, respectively). Causes of death were as expected in an SLE population with active disease receiving a wide range of standard therapies, such as corticosteroids and immunosuppressants, and included infection, cardiovascular disease, and suicide.

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in patients with SLE receiving immunosuppressant pharmacotherapy, including belimumab. Although the benefit-risk profile for belimumab remains unchanged following these events, the Sponsor considers that knowledge of these cases is important and has updated the clinical investigator's brochure (IB) for belimumab and revised the informed consent form (ICF) to communicate that development of PML is a potential risk. — Amend 03 04Feb14

Experience from open-label, long-term continuation trials of belimumab in SLE patients suggests prolonged treatment with belimumab remains generally well tolerated, with no apparent increase in the incidence of AEs or 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.

Belimumab in ANCA-Associated Vasculitis

Study Overview and Patient Population

Belimumab at a dose of 10 mg/kg in combination with standard SLE therapy demonstrated a statistically significant and clinically meaningful reduction in SLE disease activity versus placebo plus standard SLE therapy at Week 52 in two Phase 3 clinical studies in subjects with active, autoantibody-positive SLE.

Studies in subjects with WG and MPA have shown the need for more effective treatment for the maintenance of remission, with relapse rates with these 2 diseases ranging from 15% at 18 months (Jayne et al, 2003) to 38% at 3 years (Hiemstra et al, 2010) on azathioprine – the most effective of current therapies (Jayne et al, 2003; Pagnoux et al, 2008; Hiemstra et al, 2010).

The presence of ANCA autoantibodies in AAV implicates B cells in the pathogenesis of AAV. Further supporting a role for B cells is the fact that activated B cells are present in greater numbers in GPA subjects compared with healthy persons (Popa et al, 1999). Additionally, elevated levels of BLyS, a B cell survival factor, are found in subjects with AAV (Krumbholz et al, 2005; Nagai et al, 2011; Schneeweis et al, 2010). Together, these provide a strong pharmacologic rationale for the use of belimumab to treat AAV, since belimumab has been shown in SLE to reduce both B cells and autoantibody levels. Therefore, for the proposed study, subjects are required to have documented evidence of anti-PR3 or anti-MPO autoantibodies prior to randomization, as this population is considered the most likely to benefit from treatment with a B cell modulating agent like belimumab. This is consistent with the Phase 3 SLE results for belimumab where the subjects who benefitted from treatment were those who were antinuclear antibody (ANA/anti-dsDNA) autoantibody positive at baseline.

The fact that rituximab, a biologic therapy that targets B cells by binding to the B cell surface antigen CD20, recently showed success in inducing remission in AAV (Stone et al, 2010) and was granted approval in the US for the treatment of WG and MPA supports the rationale that belimumab, which down regulates B cells by targeting BLyS, may be useful in the treatment of this disease. Finally, limited data from the small (n = 111) subset of subjects in the Phase 3 trials of SLE who had vasculitic symptoms as part of their SLE (as assessed by the SELENA SLEDAI) showed that more subjects in the belimumab plus standard of care treatment arms had resolution of their vasculitic symptoms at Week 52 compared with subjects receiving placebo plus standard of care. Specifically, 19/36 (52.8%) and 28/38 (73.7%) of subjects in the belimumab 1 mg/kg and 10 mg/kg dose groups, respectively, had resolution of vasculitic activity at Week 52 compared with 15/37 (40.5%) of placebo subjects. Taken together, these data support the evaluation of belimumab in AAV.

The safety of the proposed study is supported by data from the Phase 2 and 3 trials in SLE in which subjects who were receiving belimumab in combination with significant background therapies, including steroids and immunosuppressants, had an adverse event profile similar to that of subjects receiving placebo plus standard therapies.

This is a multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen. Subjects enrolled into the study must have a clinical diagnosis of WG or MPA according to the Chapel Hill criteria and must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either CYC or RTX in the 6 months leading up to randomization. Subjects treated with 1 of the following induction regimens will be eligible for participation in the study:

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- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR
- CYC 2 mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

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[*The cyclophosphamide dosing regimens are provided as targets but may be adjusted for older age, obesity, renal insufficiency, leukopenia, or other toxicities as dictated by local practice.*]

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For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 0.5-1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ≤ 10 mg/day. As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.

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Approximately 100 subjects with ANCA-vasculitis who are between 6 and 26 weeks from starting induction therapy, who achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving ≤10 mg/day prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart will be enrolled into the study. Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter. Randomization will be performed on Day 0.

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All subjects (in both the belimumab and placebo groups) will be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. For the maintenance of remission, azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine must not be initiated any later than Day 0. For subjects previously identified as

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being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset. Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above, a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis.

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV CYC vs. oral CYC vs. RTX). It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Refer to Section 4 of Protocol HGS1006-C1100 for a complete list of inclusion and exclusion criteria.

The primary efficacy endpoint is time from Day 0 to the first relapse, defined as at least 1 major BVAS item or a minimum total BVAS score of 6 or receipt of prohibited medications according to the protocol. Subjects will receive study agent (belimumab/placebo) plus AZA until the results from the primary efficacy analysis are available or until they experience a flare (relapse) as defined in the primary efficacy endpoint. The database will be locked and the primary analysis will be performed when 12 months have elapsed after the last subject is randomized. Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an attempt will be made to ascertain survival status at 12 months after the first dose of study agent.

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In consultation with the investigating physician, subjects participating in the double-blind period of the trial will have the option to continue to receive treatment with belimumab in a 6-month open label extension phase. The criteria for entry into the extension phase of the study are: (1) the safety profile of belimumab is considered to be acceptable, based on ongoing IDMC data reviews of the safety data, and other relevant safety data sources; (2) the risk-benefit profile for continuing treatment with belimumab must be favorable in the opinion of the investigator; (3) the subject will have completed the double-blind treatment period of the trial without having relapsed (as defined in the primary endpoint); (4) a favorable opinion has been obtained from the local ethics committee or IRB with respect to continuation of belimumab treatment. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months and this will be supplied by the sponsor. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety.

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Following completion of the study and, where applicable, completion of the 6-month open-label extension phase, subjects will not receive any additional treatment supplied by the sponsor. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

All subjects will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent.

Dose and Schedule

Investigational Study Agent (Belimumab or Placebo)

The dose and schedule of belimumab proposed for use in the ANCA-associated vasculitis study is the same dosage (10 mg/kg every 2 weeks for 3 doses and every 4 weeks thereafter) and route of administration (IV) as that approved for marketing. The belimumab BDS and FDP that will be used for this study is the same as that approved for marketing.

In the Phase 3 IV SLE studies, several clinical measures of improvement including the primary efficacy endpoint at Week 52 (SRI), SELENA SLEDAI reductions, severe flare risk reduction, and complement normalization generally favored the 10 mg/kg dose. Trends toward clinically significant steroid reduction were present for both doses. Additionally, there appeared to be a greater dose response in subjects with high disease and serological activity. There was no apparent dose-response in the safety profile of belimumab with both doses being generally well-tolerated. These data supported the selection of 10 mg/kg belimumab as the marketed dose in general SLE, and also support its continued evaluation in combination with standard maintenance therapies in patients with WG or MPA.

The use of placebo in this trial is considered appropriate and does not put placebo patients at undue risk because all subjects in both the placebo group and the belimumab group will receive standard of care maintenance therapies for vasculitis (ie, azathioprine or methotrexate) and, if needed, subjects will receive appropriate rescue therapy in accordance with standard clinical practice as described above.

Induction and Maintenance Regimens for ANCA-Associated Vasculitis

Subjects participating in this trial will have had a moderate to severe episode of WG or MPA that was treated with high-dose corticosteroids (HDCS) and either RTX or CYC (IV or oral) to induce the remission of the disease. Subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR   Amend 03
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- CYC 2mg/kg/day orally plus HDCS OR

- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

[*The cyclophosphamide dosing regimens are provided as targets but may be adjusted for older age, obesity, renal insufficiency, leukopenia, or other toxicities as dictated by local practice.*] Amend 03 04Feb14

For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 0.5-1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ≤ 10 mg/day. As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction. Amend 03 04Feb14

Rituximab was approved in April 2011 by the FDA for the treatment of WG and MPA. It has been used in induction of remission in AAV for a number of years, (Gorman et al, 2003, Smith et al, 2006) and 2 recent trials published in 2010 (Stone et al, 2010), demonstrated non-inferiority to induction with cyclophosphamide, the latter of these trials being used as the basis for the recent US approval. The RTX dosing regimen of 4 infusions of 375 mg/m^2 each given 1 week apart reflects the dosing regimen that is approved by the FDA for this indication. An alternative RTX induction regimen (2 infusions of 1 gram each administered 2 weeks apart) is also offered in the protocol. Although the latter regimen is not licensed as an induction therapy for ANCA-vasculitis, it is very widely used in clinical practice and clinical evidence suggests that there is no difference between the two dosing regimens in terms of duration of B-cell depletion or therapeutic efficacy efficacy (Jones et al, 2009). Amend 03 04Feb14

Cyclophosphamide (2 mg/kg/day orally or IV 15 mg every 2 weeks for 3 doses and every 3 weeks thereafter) plus prednisone has been the standard induction regimen for WG and MPA since the early 1970s when initial work by Fauci and Wolff at the National Institutes of Health showed that this regimen induced disease remission in 12/14 patients and subsequent work showed that survival rates increased 80% using this regimen in what was previously an uniformly fatal disease (Fauci and Wolff, 1973; Fauci et al, 1983; Hoffman et al, 1992; Langford, 2011). Long term continued cyclophosphamide use, however, has been associated with significant toxicities (including infection, cystitis, cytopenias, and long term complications such as myelodysplasia and bladder cancer) and mortality (Langford, 2011).

A more recent study conducted by the European Vasculitis Group (Jayne et al, 2003) showed that after initial disease remission with cyclophosphamide and steroids, subjects could be switched to azathioprine (2 mg/kg/day) without having an increased risk of relapse compared to subjects whose remission was maintained using continued cyclophosphamide treatment. An induction regimen of CYC + prednisone followed by maintenance treatment with azathioprine is now considered the standard of care, given that administration of cyclophosphamide for longer durations does not offer an advantage from an efficacy standpoint and is associated

with a greater potential for toxicity (Langford, 2011). The cyclophosphamide regimens described above are the same as those allowed in the inclusion criteria for this vasculitis study.

Once disease remission (defined as having, on 2 consecutive measurements at least 14 days apart: a BVAS v3 score of 0 and be receiving ≤ 10 mg/day of oral prednisone [or equivalent], between 6 and 26 weeks after the first dose of induction therapy) has been achieved, subject randomization into this protocol occurs. In this maintenance of remission trial, subjects will be randomized to receive a maintenance regimen of AZA (2 mg/kg/day) + placebo or AZA (2 mg/kg/day) + belimumab (10 mg/kg). Randomization in this protocol will be stratified by induction regimen.

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The primary safety population for the SLE indication, including 473 subjects who were taking azathioprine as a concomitant medication at baseline, provides a substantial amount of safety data to support the conduct of the proposed trial. For the maintenance of remission, azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy and no later than Day 0. For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset. Subjects naive to azathioprine and who experience azathioprine-related toxicity (Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT 2 times ULN, or a several gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting), following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience toxicities, a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis. The protocol instructs physicians to follow the appropriate local prescribing information for azathioprine or methotrexate (as applicable) prior to and during treatment.

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Input on selection of these standard of care regimens was obtained from international experts in vasculitis, including members of the European Vasculitis Society (EUVAS) and the Vasculitis Clinical Research Consortium (VCRC), and consensus was reached that these regimens are appropriate for this international trial.

Complete details regarding the use of concurrent medications can be found in Section 5.5 of Protocol HGS1006-C1100.

Safety Considerations

An independent Data Monitoring Committee (DMC) will review safety data on an ongoing basis until the data are locked and analyzed (after which monitoring may be assumed by an internal HGS committee). The DMC will include at least 3 physicians and a statistician, none of whom are affiliated with the Sponsor. Belimumab has not yet been studied following use of IV cyclophosphamide (CYC) or rituximab (RTX); there is limited experience with the combination of belimumab and oral CYC. As an added safety precaution, initial randomization will be limited to 40 subjects per induction regimen (40 post-RTX induction and 40 post-CYC induction). The first DMC reviews will occur after the first 20 subjects per induction regimen (RTX or IV/oral CYC) have been randomized and have had a Week 8 visit. Once the first 20 subjects randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the DMC, who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with CYC. The DMC will review the data approximately every 6 months thereafter across both induction regimens. At all times the patients, study sites and sponsor will remain blinded to treatment allocation. Investigators and IRBs/IECs will be notified of the outcome of each DMC meeting.

The DMC will be notified of:

- all unexpected causally-related SAEs that are life-threatening or result in death;
- other unexpected causally-related SAEs;
- all reports of serious infections and opportunistic infections, irrespective of relationship to study agent; and
- subjects experiencing IgG < 250 mg/dL;

within protocol-specified timeframes. Based on these data, an ad hoc DMC meeting may be called at any time (see Section 8.3 of Protocol HGS1006-C1100 for additional detail regarding the DMC).

Based on the large body of safety data from SLE patients treated with belimumab and/or the mechanism of action of belimumab as a B cell immunosuppressant, anticipated potential risks of belimumab treatment in vasculitis patents include serious infusion and hypersensitivity reactions, infections, depression-related events, and malignancy. These risks are briefly reviewed here and are detailed more fully in the belimumab Investigator's Brochure. Both investigators and subjects will be appropriately informed regarding these risks. It is noted that because of the older patient population affected by this disease, the average age of subjects anticipated to participate in this study will be older than the average age of the SLE population studied to date (mean age of ~53 years at the time of diagnosis in vasculitis (Stone et al, 2010) compared with an average age of ~38 years in controlled Phase 3 studies of belimumab in SLE). As such, patients with vasculitis may be at a greater risk for infection than the SLE patients; however, the increased monitoring for infections by both the DMC (described above) and recommended to investigators (see below) will help to ensure subject safety through timely detection, treatment and reporting of infections.

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

In order to ensure subject safety with respect to infusion and hypersensitivity reactions, the protocol excludes patients with known history of allergic reactions to human or murine proteins or monoclonal antibodies. There is currently insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions to belimumab. The protocol recommends that based on clinical judgment, premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion. Antihistamine H2-receptor antagonists (eg, ranitidine) are also permitted. Belimumab/placebo will be administered by investigators/site personnel prepared to manage infusion reactions and anaphylaxis. The infusion rate may be slowed or interrupted if the subject develops an infusion reaction. Investigators/site personnel should be aware of the risk of hypersensitivity reactions, which may present as infusion reaction, and monitor subjects closely. In the event of a serious reaction, belimumab/placebo administration must be discontinued immediately and the appropriate medical therapy administered. Per protocol, subjects are to remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase. 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. Beyond the first 2 infusions, subjects should be monitored during and for an appropriate period of time after infusion according to study sites' guidelines or standard operating procedure for IV infusions. Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

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Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in patients with SLE receiving immunosuppressant pharmacotherapy, including belimumab. Therefore, a diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The protocol requires that subjects should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy. If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

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The protocol recommends that subjects with persistent or worsening disease should receive appropriate rescue therapy in accordance with standard clinical practice, but if exceeding what is allowed per protocol, treatment with study agent (ie, belimumab or placebo) will be discontinued and the subject will be considered as having relapsed for the primary analysis. The list of prohibited medications that results in the subjects being considered as relapsed for the primary endpoint (Protocol Section 5.5.2.1), was developed because the need for the use of these agents (eg, RTX or CYC) is indicative of treatment failure (ie, disease relapse).

Moreover, concomitant use of such medications (eg, high-dose steroids) can be associated both with potent disease-modifying activity and/or significant toxicity that may introduce bias and confound interpretation of results. As such, no subject will be denied appropriate medical care for their condition due to their participation in this clinical study.

In addition, the Sponsor notes that although this is a placebo controlled trial, the sponsor does not consider that placebo patients are at undue risk because all subjects in both the placebo group and the belimumab group will receive standard of care maintenance therapies for vasculitis (ie, azathioprine or methotrexate) and, if needed, subjects will receive appropriate rescue therapy in accordance with standard clinical practice as described above.

Risk:Benefit Conclusions

In summary, the proposed Phase 3 study is a superiority study evaluating the safety and efficacy of belimumab for the maintenance of disease remission in patients with a clinical diagnosis of Wegener's granulomatosis or microscopic polyangiitis. The risk:benefit profile of 10 mg/kg IV belimumab in patients with active, autoantibody-positive SLE was demonstrated to be positive in the two Phase 3 SLE studies, thereby supporting its approval in Canada, the US, and the EU. Belimumab has already been shown to be effective in treating patients with active, autoantibody-positive SLE, a B cell mediated autoimmune disease. Like SLE, WG and MPA are also B cell mediated autoimmune diseases in which autoantibodies (in this case, against neutrophil components), are considered to be pathogenic (Popa et al, 1999). In each of these diseases, the general purpose of the therapy is similar – reducing disease activity by down regulating B cells (including autoreactive B cells) and reducing the level autoantibodies produced by those autoreactive B cell clones. Down regulating B cell numbers may also reduce inflammatory processes because of the role of B cells in antigen presentation. A limited amount of data from the IV Phase 3 studies suggests that belimumab may reduce vasculitic symptoms.

There are potential risks associated with belimumab treatment including serious infusion and hypersensitivity reactions, infections, depression-related events, and malignancy; however, in view of the serious and potentially life threatening nature of disease flares in WG and MPA, it is believed that the overall risk:benefit analysis for belimumab in the maintenance of remission in WG and MPA is favorable, especially in view of the nature of the trial as a superiority trial over a current standard of care regimen.

Appendix 13   Algorithm for Liver Chemistry Stopping and Follow-up Criteria

Liver Stopping Event Algorithm

> - **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
> - **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*
>
> *INR value not applicable to subjects on anticoagulants

> - Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.6.2.1.

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

> Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.6.2.1.

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Protocol Amendment 04 With Local Amendment 01 for Belgium, 06 July 2015
Protocol Number: HGS1006-C1100

Protocol Title: A Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. For Belgium, the protocol (Amendment 04) has been modified at the request of the coordinating investigator in Leuven and the ethics committee to re-instate a 6-month open label extension phase to the study in order to maintain consistency with earlier versions of the protocol and 'fairness' to patients.

2. It should be noted that all previous versions of the protocol (including Amendments 01, 02 and 03) had incorporated a 6-month open label extension phase, which would allow participating subjects, who had completed the double-blind phase of the trial, the opportunity to subsequently receive open-label belimumab, supplied by the sponsor, for a further 6 months.
   Although the 6-month open-label extension phase had previously been removed from the trial as part of a global protocol amendment 04 [an amendment which fundamentally changed the status of the trial from Phase 3 to 'exploratory'], ethical objections were subsequently raised in Belgium, because subjects currently enrolled onto the trial had previously been informed that there would be an opportunity to receive a 6-month extended supply of belimumab in a 6-month open-label phase. It was felt that the change to the protocol was unfair to patients in Belgium where treatment options for ANCA-vasculitis are considered to be limited.

3. Having considered the ethical objections raised in Belgium, the sponsor agrees to re-instate the 6-month open-label phase of the study for this country. The conditions for entry into the open-label phase of the study are: (i) the safety profile of belimumab is considered to be acceptable, based on ongoing IDMC reviews and other relevant safety data sources, (ii) the risk-benefit profile for continuing treatment with belimumab is considered to be favorable in the opinion of the investigating physician, (iii) the subject will have completed the double-blind treatment phase without having a disease relapse, and (iv) a favorable opinion has been obtained from the local ethics committee in Belgium with respect to extended belimumab treatment for 6 months.
   At the end of the 6-months open label extension phase, the sponsor will no longer supply belimumab to Belgium investigators. The investigators will then be responsible for ensuring that consideration has been given to the post-study care of the patient's condition.

4. To reflect these changes, Protocol Amendment 04 has been amended locally for Belgium. The changes to the various sections are detailed below and include a Time and Events Table (Table 6.3) which details the schedule for the various safety and efficacy assessments.

5. The date of Local Amendment 01 for Belgium has been added to the cover page for clarity.

Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment: 04
Date: 26 February 2014
EudraCT 2011-004569-33

Modified to:

Protocol Amendment 04
Date: 26 February 2014
EudraCT 2011-004569-33
Local Amendment 01 for Belgium, Date: 06 July 2015

Revision Chronology for HGS1006-C1100 (BEL115466)

Added row:

	Date	Document*
Local 2015N245521_00	**06 July 2015**	**Local Amendment 01 for Belgium**

Study Synopsis
Study Design and Schedule:

Paragraph 8:

Formerly:

Subjects will receive study agent (belimumab/placebo) plus AZA until the study has completed or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see below). The study will complete, the database will be locked and the primary analysis will be performed when 12 months have elapsed after the last subject is randomized.

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Modified to:

Subjects will receive study agent (belimumab/placebo) plus AZA until the study has completed or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see below). The **double-blind phase of the study** will complete, the database will be locked and the primary analysis will be performed when 12 months have elapsed after the last subject is randomized.

Added:

In consultation with the investigating physician, subjects participating in the double-blind period of the trial will have the option to continue to receive treatment with belimumab in a 6-month open label extension phase. The criteria for entry into the extension phase of the study are: (1) the safety profile of belimumab is considered to be acceptable, based on ongoing IDMC data reviews of the safety data, and other relevant safety data sources; (2) the risk-benefit profile for continuing treatment with belimumab must be favorable in the opinion of the investigator; (3) the subject will have completed the double-blind treatment period of the trial without having relapsed (as defined in the primary endpoint); (4) a favorable opinion has been obtained from the local ethics committee or IRB with respect to continuation of belimumab treatment. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months and this will be supplied by the sponsor.

Following completion of the study and, where applicable, completion of the 6-month open-label extension phase, subjects will not receive any additional treatment supplied by the sponsor. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

Section 3, Study Design
Section 3.1 Basic Design Characteristics:

Paragraph 7:

Formerly:

Subjects will receive study agent (belimumab/placebo) plus AZA until the study has completed or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1). The study will complete, the database will be locked, and the primary analysis will be performed when 12 months have elapsed after the last subject is randomized.

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Modified to:

Subjects will receive study agent (belimumab/placebo) plus AZA until the study has completed or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1). The **double-blind phase of the study** will complete, the database will be locked, and the primary analysis will be performed when 12 months have elapsed after the last subject is randomized.

Added:

In consultation with the investigating physician, subjects participating in the double-blind period of the trial will have the option to continue to receive treatment with belimumab in a 6-month open label extension phase. The criteria for entry into the extension phase of the study are: (1) the safety profile of belimumab is considered to be acceptable, based on ongoing IDMC data reviews of the safety data, and other relevant safety data sources; (2) the risk-benefit profile for continuing treatment with belimumab must be favorable in the opinion of the investigator; (3) the subject will have completed the double-blind treatment period of the trial without having relapsed (as defined in the primary endpoint); (4) a favorable opinion has been obtained from the local ethics committee or IRB with respect to continuation of belimumab treatment. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months and this will be supplied by the sponsor.

Following completion of the study and, where applicable, completion of the 6-month open-label extension phase, subjects will not receive any additional treatment supplied by the sponsor. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

Section 6 Study Procedures

Paragraph 3:

Formerly:

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

Modified to:

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

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Section 6.3 Double-Blind Treatment Phase

Paragraph 3:

Formerly:

Subjects who have not experienced a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1) will remain on double-blind treatment with study agent until the study has completed. The study will complete and the primary efficacy analysis will be performed when 12 months have elapsed following randomization of the last subject.

Modified to:

Subjects who have not experienced a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1) will remain on double-blind treatment with study agent until the study has completed. **The double-blind phase of the study** will complete and the primary efficacy analysis will be performed when 12 months have elapsed following randomization of the last subject.

Added:

In consultation with the investigating physician, subjects participating in the double-blind period of the trial will have the option to continue to receive treatment with belimumab in a 6-month open label extension phase. The criteria for entry into the extension phase of the study are: (1) the safety profile of belimumab is considered to be acceptable, based on ongoing IDMC data reviews of the safety data, and other relevant safety data sources; (2) the risk-benefit profile for continuing treatment with belimumab must be favorable in the opinion of the investigator; (3) the subject will have completed the double-blind treatment period of the trial without having relapsed (as defined in the primary endpoint); (4) a favorable opinion has been obtained from the local ethics committee or IRB with respect to continuation of belimumab treatment. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months and this will be supplied by the sponsor.

Paragraph 4:

Formerly:

Subjects will return for an Exit visit (approximately 4 weeks after the last dose of study agent), and a follow-up visit (approximately 8 weeks after the last dose of study agent).

Modified to:

Subjects **who do not enter the open-label extension** will return for an Exit visit (approximately 4 weeks after the last dose of study agent), and a follow-up visit (approximately 8 weeks after the last dose of study agent).

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Table 6.1 Double-blind Treatment Phase Year One

Footnote 11:

Formerly:

Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 4 weeks after the last dose of study agent). The Exit Visit should be completed for subjects who discontinue the double blind treatment phase early or when subjects have completed the double-blind treatment phase. Subjects who discontinue treatment but have not relapsed will remain on the double blind study visit schedule.

Modified to:

Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 4 weeks after the last dose of study agent). The Exit Visit should **only** be completed for subjects who discontinue the double blind treatment phase early or **for subjects that have successfully** completed the double-blind treatment phase **and do not wish to participate in the open label extension phase**. Subjects who discontinue treatment but have not relapsed will remain on the double blind study visit schedule. **For subjects who complete the double blind phase and enter the open label phase, refer to Table 6-3 for visit details.**

Table 6.2 Double-blind Treatment Phase Additional Years

Footnote 7:

Formerly:

Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 1-4 weeks after the last dose of study agent). The Exit Visit should be completed for subjects who discontinue the double blind treatment phase early or when subjects have completed the double-blind treatment phase.

Modified to:

Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 1-4 weeks after the last dose of study agent). The Exit Visit should **only** be completed for subjects who discontinue the double blind treatment phase early or when subjects have **successfully** completed the double-blind treatment phase **and do not wish to participate in the open label extension phase. For subjects who complete the double blind phase and enter the open label phase, refer to Table 6-3 for visit details.**

Added:

6.4 Open-Label Extension Phase

In the 6-month open-label extension, all subjects will receive 10 mg/kg belimumab every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the last dose). The first dose on the open-label extension will be given 4 weeks after completion of the

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double-blind period. Day 0 is the first visit in the extension phase of the trial and represents the first belimumab administration for placebo subjects. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.

All subjects participating in the open-label extension will continue to be monitored for efficacy and safety as per the study calendar (see Table 6-3).

During the 6-month open-label extension, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate. Prohibited medications during this phase are live vaccines, biological therapies and other investigational agents.

All subjects will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent. These visits apply to subjects who have completed as well as those who have withdrawn early from the open-label extension.

Following completion of the 6-month open-label extension phase, subjects will not receive any additional treatment supplied by the sponsor. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

Added:

Table 6.3 Open-Label Extension Phase:

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Table 6-3 Open Label Extension Phase

Study Visit	Day 0[7]	Week 4 ± 7 days	Week 8 ± 7 days	Week 12 ± 7 days	Week 16 ± 7 days	Week 20 ± 7 days	Week 24 ± 7 days	Week 28/ Exit[8]	8 Week Follow Up[9]	Un-scheduled
Clinical Assessments										
Symptom Driven Physical Exam	X	X	X	X	X	X	X	X	-	-
Weight	X	X	X	X	X	X	X	X	-	-
Vital Signs[11, 12]	X	X	X	X	X	X	X	X	X	-
Record Concurrent Medications	X	X	X	X	X	X	X	X	X	X
Assess/Record Adverse Events[1]	X	X	X	X	X	X	X	X	X	X
BVAS	X	-	-	-	-	-	X	X	-	-
VDI	X	-	-	-	-	-	X	X	-	-
Laboratory Assessments										
Labs: Hematology & Modified Chem-20 (non fasting)[2]	X	-	-	-	-	-	X	X	X	X[10]
Urine Pregnancy Test[3]	X	X	X	X	X	X	X	X	-	-
Urinary protein: urinary creatinine and creatinine clearance	X	-	-	-	-	-	X	X	-	X[10]
Immunogenicity (anti- belimumab antibodies)[4]	X	-	-	-	-	-	X	X	X	-
T cells/B cell subset	X	-	-	-	-	-	X	X	X	-
C3/C4 and ANCA	X	-	-	-	-	-	X	X	X	-
Serum IgG	-	-	X	-	-	-	X	X	-	-
Serum IgA & IgM	-	-	-	-	-	-	X	X	-	-
CRP & ESR	X	-	-	-	-	-	X	X	X	-
Protocol Treatments										
Study agent (belimumab)[5]	X	X	X	X	X	X	X	-	-	-
AZA administration[6]	X	← Throughout the Study →						X	-	-

Footnotes on next page:

Table 6-3 Footnotes:

[1]   All adverse events (AEs) and serious adverse events (SAEs) that are identified from the start of study agent administration (Day 0) through 8 weeks following administration of the last dose of study agent should be recorded on the Adverse Event Case Report Form (AE eCRF).

[2]   Refer to Appendix 6 for laboratory assessments to be completed.

[3]   Results of urine pregnancy test at subsequent visits, if required, must be available prior to dosing. See Section 6.1 (Screening Procedures) for definition of those exempted from pregnancy testing.

[4]   Immunogenicity samples are collected pre-dose at all timepoints. For any subject who had a positive antibody response at the 8-week follow-up visit (or last study visit at which immunogenicity was assessed if 8-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or after completion and/or unblinding of the study, whichever is later.

[5]   Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.

[6]   AZA/MTX continued at the discretion of the investigator.

[7]   Day 0 is first visit in the extension phase of the trial and represents the first belimumab administration for placebo subjects.

[8]   Any visit in which the subject discontinues treatment becomes the Exit visit (ie generally 1-4 weeks after the last dose of study agent).

[9]   The 8 week follow-up visit is not required for subjects who participate in the separate continuation protocol.

[10]   Hematology, Modified Chem 20, Urinary protein/urinary creatinine and creatinine clearance are not mandatory at Unscheduled Visits and should be obtained only when determined to be clinically indicated by the Principal Investigator.

[11]   Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate.

[12]   Complete prior to dosing.

6.6Laboratory Tests

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

Modified to:

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

Section 6.7 8-Week Follow-up Visit

Formerly:

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

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

Modified to:

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

Refer to the Study Calendar (see Table 6-1, Table 6-2 **and Table 6-3**) for a list of procedures required at this visit.

Appendix 12 Protocol Addendum – Benefit and Risk Assessment

Belimumab in ANCA-Associated Vasculitis

Study Overview and Patient Population

Added:

In consultation with the investigating physician, subjects participating in the double-blind period of the trial will have the option to continue to receive treatment with belimumab in a 6-month open label extension phase. The criteria for entry into the extension phase of the study are: (1) the safety profile of belimumab is considered to be acceptable, based on ongoing IDMC data reviews of the safety data, and other relevant safety data sources; (2) the risk-benefit profile for continuing treatment with belimumab

must be favorable in the opinion of the investigator; (3) the subject will have completed the double-blind treatment period of the trial without having relapsed (as defined in the primary endpoint); (4) a favorable opinion has been obtained from the local ethics committee or IRB with respect to continuation of belimumab treatment. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months and this will be supplied by the sponsor. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety.

Following completion of the study and, where applicable, completion of the 6-month open-label extension phase, subjects will not receive any additional treatment supplied by the sponsor. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

Protocol Amendment 04 With Local Amendments 01, 02 for France, 06 April 2015
Protocol Number: HGS1006-C1100

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The proposed modifications to the protocol reflect a change by the sponsor to the strategic objectives for the evaluation of belimumab in ANCA-associated vasculitis (AAV). It is proposed that the trial should be changed from a Phase 3 study to allow for an exploratory evaluation of belimumab in AAV only. There is no longer the intention to seek a licensed indication for belimumab as an adjunctive maintenance therapy in AAV on the basis of the data emerging from this study. The term "Phase 3" has been removed from the study title.
    Enrolment of subjects onto the current trial has progressed at a much slower than expected rate. Based on current enrolment projections, data outputs from the current trial would unlikely be available for review until mid-2018.
    Having reviewed the timing of the study in the context of the evolving therapy area for ANCA-associated vasculitis, the sponsor feels that the current format and design of the BREVAS trial, if driven to completion as a Phase 3 investigation, would no longer provide significant and timely new information for the vasculitis community. On the basis of the BREVAS trial data alone, even in the event of a successful outcome, it is not felt that belimumab can be sufficiently well differentiated as a concomitant therapy for remission maintenance in AAV to fulfill a significant unmet need for patients where other therapeutic options are now available (e.g., rituximab).
    As such, GSK is proposing to modify the strategic objective of the trial such that it will be conducted as an exploratory study, in which global enrolment would be restricted to approximately 100 patients (compared to the original target of approximately 300). It is planned that the data will be published in descriptive format with exploratory analyses on efficacy endpoints undertaken as appropriate. It is expected that the safety data emerging from the smaller cohort of patients in BREVAS will contribute to our understanding of belimumab safety.
2. The study design and schedule has been modified throughout the protocol to clarify that the study will no longer be driven by the requirement to achieve at least 66 relapse events. The study will complete and the primary analysis will be undertaken once 12 months have elapsed following enrolment of the last subject.
3. The protocol has been modified throughout such that subjects completing the study will no longer have the option to participate in a 6-month open-label extension following completion of the double-blind treatment phase. The section entitled "open label extension phase" (6.4) and the related time and events table (Table 6-3) has been removed.

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4. The study design schematics have been modified in the protocol by removal of the expected number of enrolled subjects; 'N=300-400' has been removed from the schematic.

5. In the statistical sections of the protocol, the sample size considerations have been modified to reflect the fact that approximately 100 patients will be recruited. The sample size is based largely on the feasibility of recruitment within a reasonable time-frame. Sample size calculations based on expected relapse rates have been removed from the protocol. The minimum detectable effect for a sample size of N=100 subjects has been determined.

    For the purposes of reporting the data, analysis of primary and secondary endpoints will be exploratory in nature. Nominal 'p' values may be reported and considered descriptive. Where appropriate point estimates and 95% confidence intervals will be constructed.

    The section on "Subgroup analyses" (8.5.2.1) has been removed as this is no longer considered relevant in the context of the smaller expected total sample size of approximately 100 subjects.

    In the section "Primary Efficacy Analysis" (8.5.2), we have clarified how stratification terms may be handled in the analysis if there are fewer than 5 events (relapses) in any of the stratification levels.

6. In the section "Dose, route of administration and schedule", we have clarified that the administration of belimumab/placebo should be over approximately one hour, but not less than one hour for reasons of safety.

7. The section on liver chemistry stopping and follow-up criteria, which describes how patient care should be managed if a liver event occurs during the study, has been updated with the most recent GSK-specified protocol for managing these events. The section also defines the circumstances and criteria that may allow a study treatment restart following a liver event. The section also includes the criteria for more intensive monitoring with continued therapy following a liver event. Accompanying figures have been placed in Appendix 13.

8. The adverse event reporting section (Section 7) has been modified throughout for consistency with AE, SAE or PSE data collection procedures and forms.

9. The text on progressive multifocal leukoencephalopathy (PML) has been updated to provide further guidance on the management of suspected cases.

10. The section "Reporting a pregnancy" has been modified to provide scope for following up the outcomes of a pregnancy (including premature termination) as well as the status of mother and child.

11. The reference list has been updated in the protocol.

13. Appendix 12 (Benefit-Risk assessment) has been updated to reflect the change in study status to an exploratory trial and to reflect the changes in the main protocol as outlined above.

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Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment 03
Date: 04 February 2014
EudraCT 2011-004569-33
Local Amendment 02 for France, Date: 02 February 2015
Local Amendment 01 for France, Date: 01 October 2014

Modified to:

Protocol Amendment 0**4**
Date: **06 April 2015**
EudraCT 2011-004569-33
Local Amendment 02 for France, Date: 02 February 2015
Local Amendment 01 for France, Date: 01 October 2014

Title of Study, Cover Page and Synopsis

Change from:

A ~~Phase 3,~~ Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Change to:

A Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Revision Chronology for HGS1006-C1100 (BEL115466)

Added rows:

	Date	Document*
Global DNG2013N167980_02	**26 February 2015**	**Amendment No 04**

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Local   06 April 2015   **Amendment No 04 with Local Am01,**
DNG2014N217970_02   **Am02 for France**

Study Design and Schedule, Synopsis and Section 3.1, Basic Design Characteristics

Change from:

This is a ~~Phase 3~~, multi-center, multi-national, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

Change to:

This is a multi-center, multi-national, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

Change from:

Subjects will receive study agent (belimumab/placebo) plus AZA until ~~the results from the primary efficacy analysis are available~~ or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see below). The database will be locked and the primary analysis will be performed ~~after at least 66 subjects have experienced a relapse and at least~~ when 12 months have elapsed after the last subject is randomized.

Change to:

Subjects will receive study agent (belimumab/placebo) plus AZA until **the study has completed** or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see below). **The study will complete,** the database will be locked and the primary analysis will be performed **when** 12 months have elapsed after the last subject is randomized.

Study Design and Schedule, Synopsis

Deleted:

~~If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given~~

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~~the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months and this will be supplied by the sponsor. After the 6-month open-label extension phase, subjects who wish to continue treatment may do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may continue to receive belimumab under a separate continuation protocol. A separate informed consent will need to be provided for the continuation protocol. The 8-week follow-up visit is not required for subjects entering the continuation protocol.~~

Schematic of study design, Synopsis and Section 3.1, Basic Design Characteristics

Change from:

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Change to (removed number of subjects randomized from graphic):

Sample Size Considerations, Synopsis and Section 8.4, Sample Size Rationale

Deleted:

~~The relapse rate in the study is anticipated to be approximately 20% in the control group. However, there is some uncertainty around this relapse event rate which could be 30% or higher. This study is designed to target at least 66 subjects experiencing a relapse (as defined in the primary endpoint), which will provide 85% power to detect a reduction in relapse rates of 20 vs. 10% (hazard ratio = 0.472). With this same hazard ratio and a 30% event rate, a study with 66 subjects experiencing a relapse will provide 85% power to detect a reduction in the relapse rate from 30% to 15.5%. A target of 300 to 400 subjects will be randomized to achieve the required number of events.~~

~~After approximately 300 subjects have been randomized, the relapse rate in the overall population will be evaluated in a blinded manner internally by HGS while the enrollment continues. If the relapse rate is consistent with the 20% control rate assumption, enrollment will continue to 400 subjects to ensure timely accrual of the 66 events. However, if there is evidence that the relapse rate is higher than 20% control rate assumption, enrollment may be stopped at approximately 300 subjects. The primary efficacy analysis will be performed after at least 66 subjects have experienced a relapse and at least 12 months have elapsed after the last subject is randomized.~~

Added:

Approximately 100 subjects will be randomized. The sample size has been determined based on the feasibility of enrolling patients into the study within a reasonable time-frame. The sample size was not based on statistical considerations and the analysis of

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primary and secondary endpoints will be exploratory in nature. The primary efficacy analysis will be performed after 12 months have elapsed following randomization of the last subject.

Although the sample size is based on feasibility, the minimal detectable effect has been determined. Assuming an observed relapse rate at 18 months of 20% in the placebo group, a relapse rate of ≤7.0% on belimumab (hazard ratio ≤0.32) would be statistically significant (p<0.05) in a study of 100 subjects (50 per arm).

Analysis of Primary Efficacy Endpoint, Synopsis

Change from:

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The primary efficacy analysis will be performed after ~~at least 66 subjects have experienced a relapse~~ and at least 12 months have elapsed ~~after the last subject is randomized~~.

Change to:

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The primary efficacy analysis will be performed after 12 months have elapsed **following randomization of the last subject**.

Analysis of Major Secondary Efficacy Endpoints, Synopsis

Deleted:

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

Section 3.1, Basic Design Characteristics

Deleted:

~~If the result on the primary efficacy endpoint from the double-blind portion of this trial shows that belimumab is superior to placebo, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional~~

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~~6 months and this will be supplied by the sponsor. After the 6-month open-label extension phase, subjects who wish to continue treatment may do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may continue to receive belimumab under a separate continuation protocol. A separate informed consent will need to be provided for the continuation protocol. The 8 week follow-up visit is not required for subjects entering the continuation protocol.~~

Section 5.3 Dose, Route of Administration, and Schedule

Change from:

The treatment groups include one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving azathioprine (as described in Section 5.5.3). Belimumab/placebo will be administered intravenously over 1 hour. Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days thereafter. ~~Following the final double-blind visit, eligible subjects (see Section 6.4) will have the option to continue in the 6-month open-label extension period.~~

Change to:

The treatment groups include one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving azathioprine (as described in Section 5.5.3). Belimumab/placebo will be administered intravenously over 1 hour. **The intent of this instruction is to prevent more rapid infusion of belimumab which may result in a higher incidence of infusion reactions. Infusion time need <u>not</u> be exactly one hour as it is often difficult to so precisely adjust infusion times and there may be clinical reasons for infusions lasting longer than one hour. Therefore, the instruction should be interpreted as infusion over <u>at least</u> one hour. The target infusion time should still be approximately one hour assuming no other issues intervene.** Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days thereafter.

Change from:

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase ~~and the open-label extension.~~

Change to:

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase.

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Section 6 Study Procedures

Change from:

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

Change to:

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

Section 6.3 Double-Blind Treatment Phase

Change from:

Subjects who have not experienced a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1) will remain on double-blind treatment with study agent until ~~top line data from the primary analysis are availab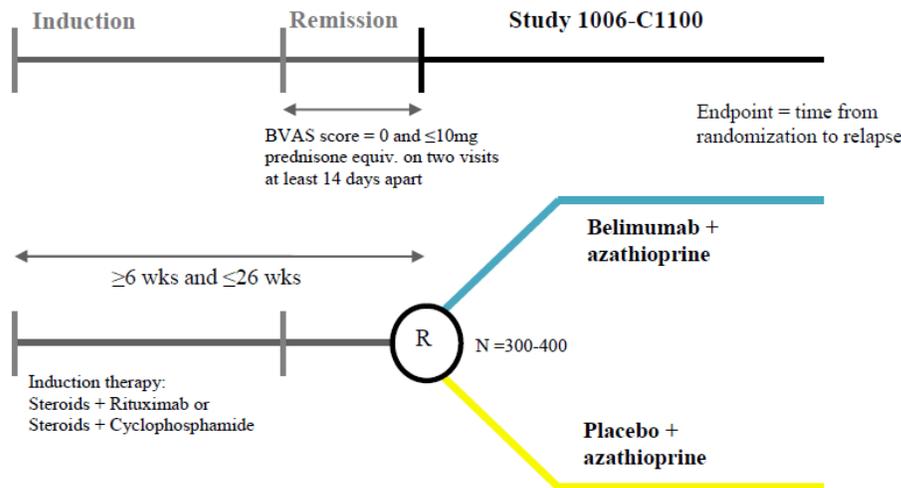le. If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who received treatment with study agent until completion of the double-blind treatment period and have not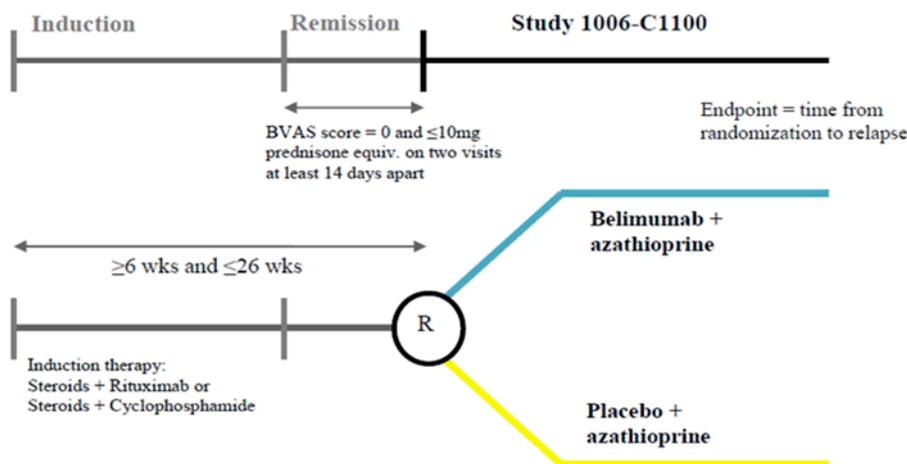 relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the 6-month open-label extension phase.~~

Subjects ~~who do not enter the open-label extension,~~ will return for an Exit visit (approximately 4 weeks after the last dose of study agent), and a follow-up visit (approximately 8 weeks after the last dose of study agent).

Change to:

Subjects who have not experienced a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1) will remain on double-blind treatment with study agent until **the study has completed. The study will complete and the primary efficacy analysis will be performed when 12 months have elapsed following randomization of the last subject.**

Subjects will return for an Exit visit (approximately 4 weeks after the last dose of study agent), and a follow-up visit (approximately 8 weeks after the last dose of study agent).

Table 6-1 Footnotes:

Change from:

11. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 4 weeks after the last dose of study agent). The Exit Visit should ~~only~~ be completed for subjects who discontinue the double blind treatment phase early or ~~for~~ subjects ~~that~~ have ~~successfully~~ completed the double-blind treatment phase ~~and do not wish to participate in the open label extension phase~~. Subjects who discontinue treatment but have not relapsed will remain on the double blind study visit schedule. ~~For subjects who complete the double blind phase and enter the open label phase, refer to Table 6-3 for visit details.~~

Change to:

11. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 4 weeks after the last dose of study agent). The Exit Visit should be completed for subjects who discontinue the double blind treatment phase early or **when** subjects have completed the double-blind treatment phase. Subjects who discontinue treatment but have not relapsed will remain on the double blind study visit schedule.

Change from:

13. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent ~~for subjects withdrawing early and those subjects who do not continue in the 6 month open-label extension phase.~~

Change to:

13. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent.

Table 6-2 Footnotes

Change from:

7. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 1-4 weeks after the last dose of study agent). The Exit Visit should ~~only~~ be completed for subjects who discontinue the double blind treatment phase early or ~~for~~ subjects ~~that~~ have ~~successfully~~ completed the double-blind treatment phase ~~and do not wish to participate in the open label extension phase. For subjects who complete the double blind phase and enter the open label phase, refer to Table 6-3 for visit details~~.

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Change to:

7. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 1-4 weeks after the last dose of study agent). The Exit Visit should be completed for subjects who discontinue the double blind treatment phase early or **when** subjects have completed the double-blind treatment phase.

Change from:

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

Change to:

9. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent.

Deleted: Section 6.4 "Open-Label Extension Phase" has been deleted and all subsequent sections have been renumbered accordingly.

6.4 Open-Label Extension Phase

In the 6-month open-label extension, all subjects will receive 10 mg/kg belimumab every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the last dose). The first dose on the open-label extension will be given 4 weeks after completion of the double-blind period. Day 0 is the first visit in the extension phase of the trial and represents the first belimumab administration for placebo subjects. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.

All subjects participating in the open-label extension will continue to be monitored for efficacy and safety as per the study calendar (see Table 6-3).

During the 6-month open-label extension, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate. Prohibited medications during this phase are live vaccines, biological therapies and other investigational agents.

All subjects will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent. These visits apply to subjects who have completed as well as those who have withdrawn early from the open-label extension.

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

Deleted:
Table 6-3 Open Label Extension Phase and all associated footnotes have been deleted
and the subsequent table has been renumbered accordingly.

Section 6.5 Laboratory Tests

Change from:

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

Change to:

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

Section 6.6.2 Phase III-IV Liver Chemistry Stopping and Follow-up Criteria

The section "Phase III-IV Liver Chemistry Stopping and Follow-up Criteria" has been deleted. The deleted text is not shown here. The section has been replaced by the following sections (6.5.2-6.5.3) and text:

6.5.2 Liver Chemistry Stopping and Follow-up Criteria

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

Liver Chemistry Stopping Criteria- Liver Stopping Event	
ALT-absolute	ALT $\geq$ 8xULN
ALT Increase	ALT $\geq$ 5xULN but <8xULN persists for $\geq$2 weeks
	ALT $\geq$ 3xULN but <5xULN persists for $\geq$4 weeks
Bilirubin[1, 2]	ALT $\geq$ 3xULN and bilirubin $\geq$ 2xULN (>35% direct bilirubin)
INR[2]	ALT $\geq$ 3xULN and INR>1.5, if INR measured
Cannot Monitor	ALT $\geq$ 5xULN but <8xULN and cannot be monitored weekly for $\geq$2 weeks

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	ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

1) Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2) All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.

3) New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

6.5.2.1 Required Actions and Follow up Assessments following ANY Liver Stopping Event

ACTIONS:

- Immediately discontinue study treatment

- Report the event to GSK **within 24 hours**

- Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE (All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants)

- Perform liver event follow up assessments

- Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below)

Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 13).

MONITORING

For bilirubin or INR criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours**

- Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline

- A specialist or hepatology consultation is recommended

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For All other criteria:
- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours**

Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline

FOLLOW UP ASSESSMENTS

- Viral hepatitis serology (includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody)

- Blood sample for pharmacokinetic (PK) analysis, obtained within approximately one to two weeks after last dose (PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Fractionate bilirubin, if total bilirubin≥2xULN

- Obtain complete blood count with differential to assess eosinophilia

- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form

- Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications

- Record alcohol use on the liver event alcohol intake case report form

For bilirubin or INR criteria:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).

- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).

Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

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6.5.3 Increased Monitoring Criteria with Continued Therapy

If met see required actions below:

- If ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks OR

- ALT ≥3xULN **and** <5xULN and bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks

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

- Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety.

- Subject can continue study treatment

- Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline

- If at any time subject meets the liver chemistry stopping criteria, proceed as described above for Required Actions and Follow up Assessments following ANY Liver Stopping Event

- If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly.

- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

Added:

6.5.4 Study Treatment Restart

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

Approval by GSK for study treatment restart can be considered where:
- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).

- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an HLA genetic

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marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.

- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.

- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.

- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.

- Study treatment must be administered at the dose specified by GSK.

- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.

- GSK to be notified of any adverse events, as per Section 7.2

Section 6.6 Exit Visit

Change from:

Refer to the Study Calendar (Table 6-1, Table 6-2 and ~~Table 6-3~~) for a list of procedures required at this visit.

Change to:

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

Section 6.7 8-Week Follow-up Visit

Change from:

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

Refer to the Study Calendar (Table 6-1, Table 6-2 and Table 6-3) for a list of procedures required at this visit.

Change to:

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

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

Section 7 Adverse Event Reporting

Added:

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

Section 7.1 Definitions

Change from:

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

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

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

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

~~+Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above (eg, possible drug-induced liver injury). These should also usually be considered serious. (ICH guidelines, March 1995)~~

~~**UNEXPECTED ADVERSE EVENT:** An adverse event, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Expected means the event has previously been observed with the study agent and is identified and/or described in the applicable product information. It does not mean that the event is expected with the underlying disease(s) or concomitant medications.~~

Change to:

ADVERSE EVENT

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

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

Events meeting the definition of an AE include:

- **Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition**

- **New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study**

- **Signs, symptoms, or the clinical sequelae of a suspected interaction**

- **Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an**

AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

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

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

- **Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE**

- **Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)**

- **Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen**

- **The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition**

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

a. **Results in** death

b. **Is** life-threatening

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

c. **Requires** hospitalisation **or** prolongation of existing hospitalisation

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

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

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

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

e. **Is a** congenital anomaly/birth defect

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

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

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

Section 7.2 Reporting Adverse Events to the Sponsor

Change from:

Serious Adverse Events (SAEs) must ALSO be recorded on the SAE ~~Worksheet and sent to the HGS Drug Safety designee~~ within 24 hours of site personnel becoming aware of the SAE, regardless of expectedness. All ~~pages~~ of the SAE ~~Worksheet~~ should be completed, but ~~the SAE Worksheet~~ should not be held until all information is available. ~~Additional~~ information and corrections should be ~~provided on subsequent SAE Worksheets~~ as described in the Study Procedures Manual. ~~SAE Worksheets should be sent either via the EDC system, if SAE EDC functionality is available or by facsimile to the HGS Drug Safety designee using the fax number listed on the SAE Worksheet~~.

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

SAEs that occur off study, after the follow-up period, that are assessed by the investigator as definitely, possibly or probably related to study agent must be reported to the ~~Drug Safety designee on the SAE worksheet. Post study SAEs will not be documented on the AE eCRF.~~

Change to:

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

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

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

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

Change from:

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

Change to:

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

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Section 7.4 Laboratory Abnormalities as Adverse Events

Change from:

A laboratory abnormality should be reported as an adverse event if it is associated with an intervention. Intervention includes, but is not limited to, discontinuation of treatment, dose reduction/delay, or concomitant therapy. In addition, any medically important laboratory abnormality may be reported as an adverse event at the discretion of the investigator. This includes laboratory abnormalities for which there is no intervention but the abnormal value(s) suggests a disease or organ toxicity. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine RBC increased). In addition, an IgG abnormality < 250 mg/dL (Grade 4) should be recorded as an adverse event (and SAE if meeting the criteria in Section 7.1).

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

Change to:

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

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

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

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Section 7.5 Progressive Multifocal Leukoencephalopathy

Change from:

If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.

Change to:

If PML is confirmed, study agent should be discontinued and consideration should be given to stopping **all** immunosuppressant therapy.

Section 7.7 Reporting a Pregnancy

Change from:

~~Pregnancies must be reported to the HGS Drug Safety designee within 24 hours of the site becoming aware of a pregnancy in a study subject. All pregnancies that are identified from the start of study agent through 16 weeks following the last dose of study agent should be reported. All pregnancies are tracked up to term or delivery following the last study agent treatment. When pregnancy is reported, HGS Drug Safety sends an acknowledgement memorandum to the principal investigator along with a Pregnancy Assessment Form. A Pregnancy Assessment Form must be completed every three months until live birth, elective termination of the pregnancy, or miscarriage. The site is responsible for following the subject's pregnancy to final outcome.~~

~~Pregnancies are not considered adverse events. Complications or medical problems associated with a pregnancy are considered AEs and may be SAEs. Complications or medical problems are reported as AEs/SAEs according to the procedure described in Section 7.1 and Section 7.2.~~

Change to:

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to the Sponsor within 2 weeks of learning of its occurrence. All pregnancies that are identified from the start of study agent through 16 weeks following the last dose of study agent should be reported. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

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

Section 7.8 Investigator Evaluation of Adverse Events

Change from:

The investigator will evaluate all adverse events with respect to seriousness, severity (intensity ~~or grade~~), and causality (relationship to study agent). ~~The criteria for serious are listed in Section 7.1. The severity of an AE is to be evaluated according to the Adverse Event Severity Grading Tables in Appendix 7. If an AE does not have Adverse Event Severity Grading in Appendix 7, the following severity classifications will be used~~:

SEVERITY:

~~Grade 1~~ **Mild**	~~- causing no limitation of usual activities.~~
~~Grade 2~~ **Moderate**	~~- causing some limitation of usual activities.~~
~~Grade 3~~ **Severe**	~~- causing inability to carry out usual activities.~~
~~Grade 4~~ **Life-threatening***	~~- potentially life-threatening or disabling; significant medical intervention is required.~~

~~*Note – a severity assessment of Life-threatening is not necessarily the same as the seriousness criterion of Life-threatening (see "serious" criteria Section 7.1). The former means that the event is a potential threat. The latter means that the event is an immediate threat to life.~~

CAUSALITY:

~~It is a regulatory requirement for investigators~~ to assess relationship between the ~~investigational product(s)~~ and the occurrence of each AE/SAE based on the information available. ~~The assessment should be reviewed on receipt of any new information and amended if necessary.~~ A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. ~~Facts/evidence or arguments that may support a "reasonable possibility" include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.~~

Change to:

The investigator will evaluate all adverse events with respect to seriousness **(criteria for seriousness are listed in Section 7.1)**, severity (intensity), and causality (relationship to study agent). **The investigator will make an assessment of intensity based on the Division of**

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Microbiology and Infectious Diseases (DMID) Adverse Event Severity Grading Tables (see Appendix 7) **where possible**:

SEVERITY:

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

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

CAUSALITY:

The investigator is obligated to assess the relationship between **study treatment** and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. **The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.**

For each AE/SAE the investigator <u>**must**</u> **document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.**

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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Section 7.9 Follow-up of Adverse Events

Change from:

~~Adverse events~~ that occur from the start of study medication through 8 weeks after the date of last administration of study agent are ~~followed until final outcome is known or until the end of the 8-week study follow-up period. Adverse events that have not resolved at the end of the 8-week study follow-up visit are recorded on the adverse event case report form (AE eCRF) as ONGOING.~~

~~SAEs that have not resolved by the end of the follow-up period are followed until final outcome of recovered or recovered with sequelae is achieved. If it is not possible to obtain a final outcome for an SAE (eg, the subject is lost to follow-up), the reason a final outcome could not be obtained will be documented by the investigator.~~

Change to:

Serious and non-serious adverse events that occur from the start of study medication **administration** through 8 weeks after the date of last administration of study agent are **reported.**

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

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

Section 8.1 General Statistical Considerations

Change from:

The database will be locked for the primary analysis after all data have been collected, verified and validated for all subjects through 12 months after the randomization of the last subject ~~or when 66 events (relapse as defined for the primary efficacy endpoint) have been observed, whichever is later~~. All subjects and study site personnel will remain blinded to original treatment assignment until after the final database is locked and the results of the study are made publicly available.

~~For the analysis of the primary and the major secondary efficacy endpoint, a step-down sequential testing procedure will be used to control the overall type 1 error. With this~~

procedure, the primary endpoint (time to the first relapse) will be evaluated first. If the primary efficacy endpoint demonstrates statistical significance (2-sided, alpha=0.05) then inference will proceed to the major secondary efficacy endpoint, time to the first major relapse (2-sided, alpha = 0.05). If the result is statistically significant, superiority of belimumab on the time to the first major relapse will be established. If statistical significance is not met, p values may be reported and considered descriptive.

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

Change to:

The database will be locked for the primary analysis after all data have been collected, verified and validated for all subjects through 12 months after the randomization of the last subject. All subjects and study site personnel will remain blinded to original treatment assignment until after the final database is locked and the results of the study are made publicly available.

Analysis of primary and secondary endpoints will be exploratory in nature. Nominal p values may be reported and considered descriptive. **Where appropriate point estimates and 95% confidence intervals will be constructed.**

Section 8.2 Randomization Procedure and Assignment to Treatment Groups

Change from:

This is a ~~Phase 3,~~ multi-center, multinational, randomized, double-blind, placebo-controlled study.

Change to:

This is a, multi-center, multinational, randomized, double-blind, placebo-controlled study.

Section 8.5.2 Primary Efficacy Analysis

Change from:

The primary efficacy analysis will compare the time to first relapse from Day 0 between the placebo/azathioprine group and the belimumab/azathioprine combination group using a Cox proportional hazard model, adjusted for ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide). However, the adjustment of induction

regimen will be changed to rituximab vs. IV and/or oral cyclophosphamide if the number of events (relapse) is less 5 in subjects using the oral or IV cyclophosphamide. For any subject who does not experience a relapse, the time to first relapse will be censored at the time of the subject's last assessment. Subjects who discontinue study agent prior to relapse/flare (as defined in primary efficacy endpoint) are to be followed per protocol for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The database will be locked and the primary efficacy analysis will be performed after ~~at least 66 subjects have experienced a relapse and at least~~ 12 months have elapsed after the last subject is randomized.

Change to:

The primary efficacy analysis will compare the time to first relapse from Day 0 between the placebo/azathioprine group and the belimumab/azathioprine combination group using a Cox proportional hazard model, adjusted for ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide). However, the adjustment of induction regimen will be changed to rituximab vs. IV and/or oral cyclophosphamide if the number of events (relapse) is less **than** 5 in subjects using the oral or IV cyclophosphamide. **If there are then still less than 5 patients with an event (relapse) in any of the levels of this or any other stratification factor then the stratification term may be removed from the model.** For any subject who does not experience a relapse, the time to first relapse will be censored at the time of the subject's last assessment. Subjects who discontinue study agent prior to relapse/flare (as defined in primary efficacy endpoint) are to be followed per protocol for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The database will be locked and the primary efficacy analysis will be performed after 12 months have elapsed **following randomization of the last subject.**

Deleted:

~~Section 8.5.2.1 Subgroup Analysis~~

~~Subgroup analysis, of the primary efficacy endpoint only, will be performed in the following subgroups:~~

- ~~ANCA type (anti-PR3 vs. anti-MPO)~~
- ~~Disease type (WG vs. MPA)~~
- ~~Disease stage at induction (initial diagnosis vs. relapsing disease)~~
- ~~Induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide)~~
- ~~Race (white, American Indian, Asian, and black)~~
- ~~Region (US/Canada, EU/Australia/Israel, Americas excluding US/Canada, and Asia)~~
- ~~Age (< 65 vs. ≥ 65)~~

- ~~Gender~~
- ~~Duration of IV corticosteroid pulse used for induction (1 day vs > 1 day)~~

Section 8.5.5 Major Secondary Endpoint analysis and Other Efficacy Analyses

Change from:

The analysis of the major secondary efficacy endpoint will be performed using the same method described for the primary efficacy endpoint, but censoring subjects who receive any prohibited medication (as defined in Section 5.5.1) prior to an observation of any major BVAS item. Any censoring will be applied on the date prohibited medications are received.

Change to:

The **exploratory** analysis of the major secondary efficacy endpoint will be performed using the same method described for the primary efficacy endpoint, but censoring subjects who receive any prohibited medication (as defined in Section 5.5.1) prior to an observation of any major BVAS item. Any censoring will be applied on the date prohibited medications are received.

References

Added:

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, Study Overview and Patient Population

Change from:

This is a ~~Phase 3,~~ multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

Change to:

This is a multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in

subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

Change from:

~~A target of 300 to 400 subjects~~ who are between 6 and 26 weeks from starting induction therapy, achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving ≤10 mg/day prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart will be enrolled into the study.

Change to:

Approximately 100 subjects with ANCA-vasculitis who are between 6 and 26 weeks from starting induction therapy, **who** achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving ≤10 mg/day prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart will be enrolled into the study.

Change from:

The database will be locked and the primary analysis will be performed ~~after at least 66 subjects have experienced a relapse and at least~~ 12 months have elapsed after the last subject is randomized.

Change to:

The database will be locked and the primary analysis will be performed **when** 12 months have elapsed after the last subject is randomized.

Deleted:

~~If top-line data from the double-blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in a 6-month open-label extension period, in which all subjects will receive 10 mg/kg belimumab IV. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety.~~

Deleted:

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

~~After the 6-month open-label extension phase, subjects who wish to continue treatment may do so by being prescribed commercially available belimumab. If belimumab is not~~

~~commercially available in a subject's country of participation, the subject may continue to receive belimumab under a separate continuation protocol. A separate informed consent will be provided for the continuation protocol. The 8 week follow-up visit is not required for subjects entering the continuation protocol.~~

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, Safety Considerations

Change from:

Per protocol, subjects are to remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase ~~and the open-label extension~~.

Change to:

Per protocol, subjects are to remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase.

Appendix 13 Algorithm for Liver Chemistry Stopping and Follow-up Criteria

Added:

Liver Stopping Event Algorithm

Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.5.2.1.

References

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

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

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

Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.5.3.1.

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Deleted:

Phase III-IV Liver Safety Algorithms

Local Amendment 02 for France, 02 February 2015
Protocol Number: HGS1006-C1100-03

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The protocol has been modified, at the request of the French National Agency for Medicines and Health Products Safety (ANSM), to limit the duration of treatment with belimumab to 3 years. Further dosing after 3 years might be possible, but only following additional approval from ANSM and re-visiting of risk-benefit at that time.

Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment: 03
Date: 04 February 2014

Modified to:

Protocol Amendment: 03
Date: 04 February 2014

Local Amendment 02 for France, Date: 02 February 2015
Local Amendment 01 for France, Date: 01 October 2014

Section 3.1 Basic Design Characteristics

Section 8.4 Sample Size Rationale

Added:

The maximum duration of treatment with study agent (belimumab/placebo) for patients enrolled onto this trial in France should not exceed 3 years in the first instance. If it is anticipated that some patient(s) would be likely to require extended treatment beyond 3 years, this will be subject to approval by the Agence nationale de sécurité du médicament et des produits de santé (ANSM), following timely submission of an application with due consideration of the risk/benefit ratio of the treatment beyond 3 years. The trial sponsor will be monitoring the duration of treatment for enrolled subjects and will advise investigators and ANSM accordingly.

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Local Amendment 01 for France, 01 October 2014
Protocol Number: HGS1006-C1100-03

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The protocol has been modified, at the request of the French National Security Agency for Medicines and Health Products (ANSM), to include guidance for French investigators to evaluate suspected cases of Progressive multifocal leukoencephalopathy (PML) using brain imaging and polymerase chain reaction (PCR) on cerebrospinal fluid for JC virus (JCV).
2. During Amendment 03, the absolute requirement to randomize within 2 weeks of confirmation of remission was removed, but a statement to this effect was inadvertently left in Section 8.2 Randomization Procedure and Assignment to Treatment Groups. The statement has now been deleted from Section 8.2.
3. In the Revision Chronology, Local Addendum 02 for Ireland was inadvertently not listed. This information has now been added. This change is not shown in the Modifications section below.
4. In Appendix 12, the cross-reference to Protocol Section "5.5.2.1" should have been to Protocol Section "5.5.1". The typographical error has now been corrected. This change is not shown in the Modifications section below.

Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment: 03
Date: 04 February 2014

Modified to:

Protocol Amendment: 03
Date: 04 February 2014

Local Amendment 01 for France, Date: 01 October 2014

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List of Abbreviations

Added:

JCV   JC virus

Section 7.5 Progressive Multifocal Leukoencephalopathy

Formerly:

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. A diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The subject should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.

If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

Modified to:

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. A diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The subject should be referred to a neurologist or other appropriate specialist for evaluation. **Evaluation of suspected PML may include the following: 1. Magnetic resonance imaging of the brain, with and without contrast enhancement; 2. Cerebrospinal fluid analysis for JCV DNA by polymerase chain reaction; 3. If these tests are negative or inconclusive, they may need to be repeated, or a brain biopsy from a region of the brain that is associated with clinical symptoms may be needed.** If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.

If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

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Section 8.2 Randomization Procedure and Assignment to Treatment Groups

Formerly:

This is a Phase 3, multi-center, multinational, randomized, double-blind, placebo-controlled study. Once subjects have consented, have undergone all screening procedures and have been determined to be eligible for the study, they will be randomly assigned (via an interactive web response system [IWRS]) to 1 of 2 treatment groups (belimumab [10 mg/kg] or placebo) in a 1:1 ratio. At randomization, subjects will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. RTX). Randomization will be performed on Day 0. ~~Day 0 (first administration of belimumab/placebo and azathioprine) must occur no more than 2 weeks after confirmation of remission.~~

Modified to:

This is a Phase 3, multi-center, multinational, randomized, double-blind, placebo-controlled study. Once subjects have consented, have undergone all screening procedures and have been determined to be eligible for the study, they will be randomly assigned (via an interactive web response system [IWRS]) to 1 of 2 treatment groups (belimumab [10 mg/kg] or placebo) in a 1:1 ratio. At randomization, subjects will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. RTX). Randomization will be performed on Day 0.

Protocol Amendment 04 With Local Addenda 01, 02 for Ireland, 06 April 2015
Protocol Number: HGS1006-C1100

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The proposed modifications to the protocol reflect a change by the sponsor to the strategic objectives for the evaluation of belimumab in ANCA-associated vasculitis (AAV). It is proposed that the trial should be changed from a Phase 3 study to allow for an exploratory evaluation of belimumab in AAV only. There is no longer the intention to seek a licensed indication for belimumab as an adjunctive maintenance therapy in AAV on the basis of the data emerging from this study. The term "Phase 3" has been removed from the study title.
   Enrolment of subjects onto the current trial has progressed at a much slower than expected rate. Based on current enrolment projections, data outputs from the current trial would unlikely be available for review until mid-2018.
   Having reviewed the timing of the study in the context of the evolving therapy area for ANCA-associated vasculitis, the sponsor feels that the current format and design of the BREVAS trial, if driven to completion as a Phase 3 investigation, would no longer provide significant and timely new information for the vasculitis community. On the basis of the BREVAS trial data alone, even in the event of a successful outcome, it is not felt that belimumab can be sufficiently well differentiated as a concomitant therapy for remission maintenance in AAV to fulfill a significant unmet need for patients where other therapeutic options are now available (e.g., rituximab).
   As such, GSK is proposing to modify the strategic objective of the trial such that it will be conducted as an exploratory study, in which global enrolment would be restricted to approximately 100 patients (compared to the original target of approximately 300). It is planned that the data will be published in descriptive format with exploratory analyses on efficacy endpoints undertaken as appropriate. It is expected that the safety data emerging from the smaller cohort of patients in BREVAS will contribute to our understanding of belimumab safety.

2. The study design and schedule has been modified throughout the protocol to clarify that the study will no longer be driven by the requirement to achieve at least 66 relapse events. The study will complete and the primary analysis will be undertaken once 12 months have elapsed following enrolment of the last subject.

3. The protocol has been modified throughout such that subjects completing the study will no longer have the option to participate in a 6-month open-label extension following completion of the double-blind treatment phase. The section entitled "open label extension phase" (6.4) and the related time and events table (Table 6-3) has been removed.

4. The study design schematics have been modified in the protocol by removal of the expected number of enrolled subjects; 'N=300-400' has been removed from the schematic.

5. In the statistical sections of the protocol, the sample size considerations have been modified to reflect the fact that approximately 100 patients will be recruited. The sample size is based largely on the feasibility of recruitment within a reasonable time-frame. Sample size calculations based on expected relapse rates have been removed from the protocol. The minimum detectable effect for a sample size of N=100 subjects has been determined.

   For the purposes of reporting the data, analysis of primary and secondary endpoints will be exploratory in nature. Nominal 'p' values may be reported and considered descriptive. Where appropriate point estimates and 95% confidence intervals will be constructed.

   The section on "Subgroup analyses" (8.5.2.1) has been removed as this is no longer considered relevant in the context of the smaller expected total sample size of approximately 100 subjects.

   In the section "Primary Efficacy Analysis" (8.5.2), we have clarified how stratification terms may be handled in the analysis if there are fewer than 5 events (relapses) in any of the stratification levels.

6. In the section "Dose, route of administration and schedule", we have clarified that the administration of belimumab/placebo should be over approximately one hour, but not less than one hour for reasons of safety.

7. The section on liver chemistry stopping and follow-up criteria, which describes how patient care should be managed if a liver event occurs during the study, has been updated with the most recent GSK-specified protocol for managing these events. The section also defines the circumstances and criteria that may allow a study treatment restart following a liver event. The section also includes the criteria for more intensive monitoring with continued therapy following a liver event. Accompanying figures have been placed in Appendix 13.

8. The adverse event reporting section (Section 7) has been modified throughout for consistency with AE, SAE or PSE data collection procedures and forms.

9. The text on progressive multifocal leukoencephalopathy (PML) has been updated to provide further guidance on the management of suspected cases.

10. The section "Reporting a pregnancy" has been modified to provide scope for following up the outcomes of a pregnancy (including premature termination) as well as the status of mother and child.

11. The section "Randomization procedure and assignment to treatment requirements" has been modified to remove the requirement for subjects to be randomised within 2 weeks of achieving remission. This corrects an error in the protocol and ensures consistency with wording across other sections of the protocol.

12. The reference list has been updated in the protocol.

13. Appendix 12 (Benefit-Risk assessment) has been updated to reflect the change in study status to an exploratory trial and to reflect the changes in the main protocol as outlined above.

Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment 0**3**
Date: 25 February 2014
EudraCT 2011-004569-33
Local Addendum 01 for Ireland, Date: 31 January 2013
Local Addendum 02 for Ireland, Date: 07 August 2013

Modified to:

Protocol Amendment 0**4**
Date: **06 April 2015**
EudraCT 2011-004569-33
Local Addendum 01 for Ireland, Date: 31 January 2013
Local Addendum 02 for Ireland, Date: 07 August 2013

Title of Study, Cover Page and Synopsis

Change from:

A ~~Phase 3,~~ Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Change to:

A Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Revision Chronology for HGS1006-C1100 (BEL115466)

Added rows:

	Date	Document*
Local DNG2014N217970_01	**01 October 2014**	**Local Amendment 01 for France**

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Local **DNG2014N217970_02**	**03 February 2015**	**Local Amendment 02for France**
Global **DNG2013N167980_02**	**26 February 2015**	**Amendment No 04**
Local **DNG2013N160488_04**	**06 April 2015**	**Amendment No 04 with Addendum** **01, 02 for Ireland**

Study Design and Schedule, Synopsis and Section 3.1, Basic Design Characteristics

Change from:

This is a ~~Phase 3~~, multi-center, multi-national, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

Change to:

This is a multi-center, multi-national, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

Change from:

Subjects will receive study agent (belimumab/placebo) plus AZA until ~~the results from the primary efficacy analysis are available~~ or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see below). The database will be locked and the primary analysis will be performed ~~after at least 66 subjects have experienced a relapse and at least~~ when 12 months have elapsed after the last subject is randomized.

Change to:

Subjects will receive study agent (belimumab/placebo) plus AZA until **the study has completed** or until they experience a flare (relapse) as defined in the primary efficacy endpoint (see below). **The study will complete,** the database will be locked and the primary analysis will be performed **when** 12 months have elapsed after the last subject is randomized.

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Study Design and Schedule, Synopsis

Deleted:

~~If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months and this will be supplied by the sponsor. After the 6-month open-label extension phase, subjects who wish to continue treatment may do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may continue to receive belimumab under a separate continuation protocol. A separate informed consent will need to be provided for the continuation protocol. The 8-week follow-up visit is not required for subjects entering the continuation protocol.~~

Schematic of study design, Synopsis and Section 3.1, Basic Design Characteristics

Change from:

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Change to (removed number of subjects randomized from graphic):

Sample Size Considerations, Synopsis and Section 8.4, Sample Size Rationale

Deleted:

The relapse rate in the study is anticipated to be approximately 20% in the control group. However, there is some uncertainty around this relapse event rate which could be 30% or higher. This study is designed to target at least 66 subjects experiencing a relapse (as defined in the primary endpoint), which will provide 85% power to detect a reduction in relapse rates of 20 vs. 10% (hazard ratio = 0.472). With this same hazard ratio and a 30% event rate, a study with 66 subjects experiencing a relapse will provide 85% power to detect a reduction in the relapse rate from 30% to 15.5%. A target of 300 to 400 subjects will be randomized to achieve the required number of events.

After approximately 300 subjects have been randomized, the relapse rate in the overall population will be evaluated in a blinded manner internally by HGS while the enrollment continues. If the relapse rate is consistent with the 20% control rate assumption, enrollment will continue to 400 subjects to ensure timely accrual of the 66 events. However, if there is evidence that the relapse rate is higher than 20% control rate assumption, enrollment may be stopped at approximately 300 subjects. The primary efficacy analysis will be performed after at least 66 subjects have experienced a relapse and at least 12 months have elapsed after the last subject is randomized.

Added:

Approximately 100 subjects will be randomized. The sample size has been determined based on the feasibility of enrolling patients into the study within a reasonable time-frame. The sample size was not based on statistical considerations and the analysis of

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primary and secondary endpoints will be exploratory in nature. The primary efficacy analysis will be performed after 12 months have elapsed following randomization of the last subject.

Although the sample size is based on feasibility, the minimal detectable effect has been determined. Assuming an observed relapse rate at 18 months of 20% in the placebo group, a relapse rate of ≤7.0% on belimumab (hazard ratio ≤0.32) would be statistically significant (p<0.05) in a study of 100 subjects (50 per arm).

Analysis of Primary Efficacy Endpoint, Synopsis

Change from:

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The primary efficacy analysis will be performed after ~~at least 66 subjects have experienced a relapse~~ and at least 12 months have elapsed ~~after the last subject is randomized~~.

Change to:

Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The primary efficacy analysis will be performed after 12 months have elapsed **following randomization of the last subject**.

Analysis of Major Secondary Efficacy Endpoints, Synopsis

Deleted:

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

Section 3.1, Basic Design Characteristics

Deleted:

~~If the result on the primary efficacy endpoint from the double-blind portion of this trial shows that belimumab is superior to placebo, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional~~

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~~6 months and this will be supplied by the sponsor. After the 6-month open-label extension phase, subjects who wish to continue treatment may do so by being prescribed commercially available belimumab. If belimumab is not commercially available in a subject's country of participation, the subject may continue to receive belimumab under a separate continuation protocol. A separate informed consent will need to be provided for the continuation protocol. The 8 week follow-up visit is not required for subjects entering the continuation protocol.~~

Section 5.3 Dose, Route of Administration, and Schedule

Change from:

The treatment groups include one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving azathioprine (as described in Section 5.5.3). Belimumab/placebo will be administered intravenously over 1 hour. Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days thereafter. ~~Following the final double-blind visit, eligible subjects (see Section 6.4) will have the option to continue in the 6-month open-label extension period.~~

Change to:

The treatment groups include one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving azathioprine (as described in Section 5.5.3). Belimumab/placebo will be administered intravenously over 1 hour. **The intent of this instruction is to prevent more rapid infusion of belimumab which may result in a higher incidence of infusion reactions. Infusion time need <u>not</u> be exactly one hour as it is often difficult to so precisely adjust infusion times and there may be clinical reasons for infusions lasting longer than one hour. Therefore, the instruction should be interpreted as infusion over <u>at least</u> one hour. The target infusion time should still be approximately one hour assuming no other issues intervene.** Once randomized, subjects will be dosed with study agent on Days 0, 14, and 28 and every 28 days thereafter.

Change from:

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase ~~and the open-label extension.~~

Change to:

In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase.

Section 6 Study Procedures

Change from:

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

Change to:

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

Section 6.3 Double-Blind Treatment Phase

Change from:

Subjects who have not experienced a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1) will remain on double-blind treatment with study agent until ~~top line data from the primary analysis are available. If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who received treatment with study agent until completion of the double-blind treatment period and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the 6-month open-label extension phase.~~

Subjects ~~who do not enter the open-label extension,~~ will return for an Exit visit (approximately 4 weeks after the last dose of study agent), and a follow-up visit (approximately 8 weeks after the last dose of study agent).

Change to:

Subjects who have not experienced a flare (relapse) as defined in the primary efficacy endpoint (see Section 8.5.1) will remain on double-blind treatment with study agent until **the study has completed. The study will complete and the primary efficacy analysis will be performed when 12 months have elapsed following randomization of the last subject.**

Subjects will return for an Exit visit (approximately 4 weeks after the last dose of study agent), and a follow-up visit (approximately 8 weeks after the last dose of study agent).

Table 6-1 Footnotes:

Change from:

11. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 4 weeks after the last dose of study agent). The Exit Visit should ~~only~~ be completed for subjects who discontinue the double blind treatment phase early or ~~for~~ subjects ~~that~~ have ~~successfully~~ completed the double-blind treatment phase ~~and do not wish to participate in the open label extension phase~~. Subjects who discontinue treatment but have not relapsed will remain on the double blind study visit schedule. ~~For subjects who complete the double blind phase and enter the open label phase, refer to Table 6-3 for visit details.~~

Change to:

11. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 4 weeks after the last dose of study agent). The Exit Visit should be completed for subjects who discontinue the double blind treatment phase early or **when** subjects have completed the double-blind treatment phase. Subjects who discontinue treatment but have not relapsed will remain on the double blind study visit schedule.

Change from:

13. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent ~~for subjects withdrawing early and those subjects who do not continue in the 6 month open-label extension phase.~~

Change to:

13. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent.

Table 6-2 Footnotes

Change from:

7. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 1-4 weeks after the last dose of study agent). The Exit Visit should ~~only~~ be completed for subjects who discontinue the double blind treatment phase early or ~~for~~ subjects ~~that~~ have ~~successfully~~ completed the double-blind treatment phase ~~and do not wish to participate in the open label extension phase. For subjects who complete the double blind phase and enter the open label phase, refer to Table 6-3 for visit details~~.

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Change to:

7. Any visit in which the subject discontinues treatment becomes the Exit visit (ie, generally 1-4 weeks after the last dose of study agent). The Exit Visit should be completed for subjects who discontinue the double blind treatment phase early or **when** subjects have completed the double-blind treatment phase.

Change from:

9. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent ~~for subjects withdrawing early and those subjects who do not continue in the 6 month open-label extension phase~~.

Change to:

9. The 8 week follow-up visit is to occur approximately 8 weeks after the last dose of study agent.

Deleted: Section 6.4 "Open-Label Extension Phase" has been deleted and all subsequent sections have been renumbered accordingly.

~~6.4 Open-Label Extension Phase~~

~~In the 6-month open-label extension, all subjects will receive 10 mg/kg belimumab every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the last dose). The first dose on the open-label extension will be given 4 weeks after completion of the double-blind period. Day 0 is the first visit in the extension phase of the trial and represents the first belimumab administration for placebo subjects. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.~~

~~All subjects participating in the open-label extension will continue to be monitored for efficacy and safety as per the study calendar (see Table 6-3).~~

~~During the 6-month open-label extension, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically appropriate. Prohibited medications during this phase are live vaccines, biological therapies and other investigational agents.~~

~~All subjects will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent. These visits apply to subjects who have completed as well as those who have withdrawn early from the open-label extension.~~

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

Deleted:
Table 6-3 Open Label Extension Phase and all associated footnotes have been deleted *and the subsequent table has been renumbered accordingly.*

Section 6.5 Laboratory Tests

Change from:

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

Change to:

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

Section 6.6.2 Phase III-IV Liver Chemistry Stopping and Follow-up Criteria

The section "Phase III-IV Liver Chemistry Stopping and Follow-up Criteria" has been deleted. The deleted text is not shown here. The section has been replaced by the following sections (6.5.2-6.5.3) and text:

6.5.2 Liver Chemistry Stopping and Follow-up Criteria

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

Liver Chemistry Stopping Criteria- Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
	ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN and INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks

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	ALT $\geq$ 3xULN but <5xULN and cannot be monitored weekly for $\geq$4 weeks
Symptomatic[3]	ALT $\geq$ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

1) Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT $\geq$ 3xULN **and** bilirubin $\geq$ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2) All events of ALT $\geq$ 3xULN **and** bilirubin $\geq$ 2xULN (>35% direct bilirubin) or ALT $\geq$ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.

3) New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

6.5.2.1 Required Actions and Follow up Assessments following ANY Liver Stopping Event

ACTIONS:

- Immediately discontinue study treatment

- Report the event to GSK **within 24 hours**

- Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE (All events of ALT $\geq$ 3xULN and bilirubin $\geq$ 2xULN (>35% direct bilirubin) or ALT $\geq$ 3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants)

- Perform liver event follow up assessments

- Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below)

Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 13).

MONITORING

For bilirubin or INR criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours**

- Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline

- A specialist or hepatology consultation is recommended

For All other criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours**

Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline

FOLLOW UP ASSESSMENTS

- Viral hepatitis serology (includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody)

- Blood sample for pharmacokinetic (PK) analysis, obtained within approximately one to two weeks after last dose (PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Fractionate bilirubin, if total bilirubin≥2xULN

- Obtain complete blood count with differential to assess eosinophilia

- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form

- Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications

- Record alcohol use on the liver event alcohol intake case report form

For bilirubin or INR criteria:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).

- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).

Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

6.5.3 Increased Monitoring Criteria with Continued Therapy

If met see required actions below:

- If ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks OR

- ALT ≥3xULN **and** <5xULN and bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks

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

- Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety.

- Subject can continue study treatment

- Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline

- If at any time subject meets the liver chemistry stopping criteria, proceed as described above for Required Actions and Follow up Assessments following ANY Liver Stopping Event

- If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly.

- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

Added:

6.5.4 Study Treatment Restart

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

Approval by GSK for study treatment restart can be considered where:
- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).

- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an HLA genetic

marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.

- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.

- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.

- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.

- Study treatment must be administered at the dose specified by GSK.

- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.

- GSK to be notified of any adverse events, as per Section 7.2

Section 6.6 Exit Visit

Change from:

Refer to the Study Calendar (Table 6-1, Table 6-2 and ~~Table 6-3~~) for a list of procedures required at this visit.

Change to:

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

Section 6.7 8-Week Follow-up Visit

Change from:

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

Refer to the Study Calendar (Table 6-1, Table 6-2 and Table 6-3) for a list of procedures required at this visit.

Change to:

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

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

Section 7 Adverse Event Reporting

Added:

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

Section 7.1 Definitions

Change from:

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

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

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

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

+Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above (eg, possible drug-induced liver injury). These should also usually be considered serious. (ICH guidelines, March 1995)

UNEXPECTED ADVERSE EVENT: An adverse event, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Expected means the event has previously been observed with the study agent and is identified and/or described in the applicable product information. It does not mean that the event is expected with the underlying disease(s) or concomitant medications.

Change to:

ADVERSE EVENT

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

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

Events meeting the definition of an AE include:

- **Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition**

- **New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study**

- **Signs, symptoms, or the clinical sequelae of a suspected interaction**

- **Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an**

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AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

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

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

- **Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE**

- **Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)**

- **Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen**

- **The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition**

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

a. **Results in** death

b. **Is** life-threatening

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

c. **Requires** hospitalisation **or** prolongation of existing hospitalisation

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

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

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

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

e. **Is a** congenital anomaly/birth defect

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

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

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

Section 7.2 Reporting Adverse Events to the Sponsor

Change from:

Serious Adverse Events (SAEs) must ALSO be recorded on the SAE ~~Worksheet and sent to the HGS Drug Safety designee~~ within 24 hours of site personnel becoming aware of the SAE, regardless of expectedness. All ~~pages~~ of the SAE ~~Worksheet~~ should be completed, but ~~the SAE Worksheet~~ should not be held until all information is available. ~~Additional~~ information and corrections should be ~~provided on subsequent SAE Worksheets~~ as described in the Study Procedures Manual. ~~SAE Worksheets should be sent either via the EDC system, if SAE EDC functionality is available or by facsimile to the HGS Drug Safety designee using the fax number listed on the SAE Worksheet~~.

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

SAEs that occur off study, after the follow-up period, that are assessed by the investigator as definitely, possibly or probably related to study agent must be reported to the ~~Drug Safety designee on the SAE worksheet. Post study SAEs will not be documented on the AE eCRF.~~

Change to:

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

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

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

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

Change from:

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

Change to:

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

Section 7.4 Laboratory Abnormalities as Adverse Events

Change from:

A laboratory abnormality should be reported as an adverse event if it is associated with an intervention. Intervention includes, but is not limited to, discontinuation of treatment, dose reduction/delay, or concomitant therapy. In addition, any medically important laboratory abnormality may be reported as an adverse event at the discretion of the investigator. This includes laboratory abnormalities for which there is no intervention but the abnormal value(s) suggests a disease or organ toxicity. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine RBC increased). In addition, an IgG abnormality < 250 mg/dL (Grade 4) should be recorded as an adverse event (and SAE if meeting the criteria in Section 7.1).

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

Change to:

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

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

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

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Section 7.5 Progressive Multifocal Leukoencephalopathy

Change from:

If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.

Change to:

If PML is confirmed, study agent should be discontinued and consideration should be given to stopping **all** immunosuppressant therapy.

Section 7.7 Reporting a Pregnancy

Change from:

Pregnancies must be reported to the HGS Drug Safety designee within 24 hours of the site becoming aware of a pregnancy in a study subject. All pregnancies that are identified from the start of study agent through 16 weeks following the last dose of study agent should be reported. All pregnancies are tracked up to term or delivery following the last study agent treatment. When pregnancy is reported, HGS Drug Safety sends an acknowledgement memorandum to the principal investigator along with a Pregnancy Assessment Form. A Pregnancy Assessment Form must be completed every three months until live birth, elective termination of the pregnancy, or miscarriage. The site is responsible for following the subject's pregnancy to final outcome.

Pregnancies are not considered adverse events. Complications or medical problems associated with a pregnancy are considered AEs and may be SAEs. Complications or medical problems are reported as AEs/SAEs according to the procedure described in Section 7.1 and Section 7.2.

Change to:

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to the Sponsor within 2 weeks of learning of its occurrence. All pregnancies that are identified from the start of study agent through 16 weeks following the last dose of study agent should be reported. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

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

Section 7.8 Investigator Evaluation of Adverse Events

Change from:

The investigator will evaluate all adverse events with respect to seriousness, severity (intensity ~~or grade~~), and causality (relationship to study agent). ~~The criteria for serious are listed in Section 7.1. The severity of an AE is to be evaluated according to the Adverse Event Severity Grading Tables in Appendix 7. If an AE does not have Adverse Event Severity Grading in Appendix 7, the following severity classifications will be used~~:

SEVERITY:

~~Grade 1~~ **Mild**	— ~~causing no limitation of usual activities.~~	
~~Grade 2~~ **Moderate**	— ~~causing some limitation of usual activities.~~	
~~Grade 3~~ **Severe**	— ~~causing inability to carry out usual activities.~~	
~~Grade 4~~ **Life-threatening***	- ~~potentially life-threatening or disabling; significant medical intervention is required.~~	

~~*Note – a severity assessment of Life-threatening is not necessarily the same as the seriousness criterion of Life-threatening (see "serious" criteria Section 7.1). The former means that the event is a potential threat. The latter means that the event is an immediate threat to life.~~

CAUSALITY:

~~It is a regulatory requirement for investigators~~ to assess relationship between the ~~investigational product(s)~~ and the occurrence of each AE/SAE based on the information available. ~~The assessment should be reviewed on receipt of any new information and amended if necessary.~~ A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. ~~Facts/evidence or arguments that may support a "reasonable possibility" include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.~~

Change to:

The investigator will evaluate all adverse events with respect to seriousness **(criteria for seriousness are listed in Section 7.1)**, severity (intensity), and causality (relationship to study agent). **The investigator will make an assessment of intensity based on the Division of**

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Microbiology and Infectious Diseases (DMID) Adverse Event Severity Grading Tables (see Appendix 7) **where possible**:

SEVERITY:

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

- Moderate   **An event that is sufficiently discomforting to interfere with everyday activities (Grade 2 DMID).**

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

- **Not applicable**   **Those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).**

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

CAUSALITY:

The investigator is obligated to assess the relationship between **study treatment** and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. **The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.**

For each AE/SAE the investigator <u>must</u> document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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Section 7.9 Follow-up of Adverse Events

Change from:

~~Adverse events~~ that occur from the start of study medication through 8 weeks after the date of last administration of study agent are ~~followed until final outcome is known or until the end of the 8-week study follow-up period. Adverse events that have not resolved at the end of the 8-week study follow-up visit are recorded on the adverse event case report form (AE eCRF) as ONGOING.~~

~~SAEs that have not resolved by the end of the follow-up period are followed until final outcome of recovered or recovered with sequelae is achieved. If it is not possible to obtain a final outcome for an SAE (eg, the subject is lost to follow-up), the reason a final outcome could not be obtained will be documented by the investigator~~.

Change to:

Serious and non-serious adverse events that occur from the start of study medication **administration** through 8 weeks after the date of last administration of study agent are **reported.**

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

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

Section 8.1 General Statistical Considerations

Change from:

The database will be locked for the primary analysis after all data have been collected, verified and validated for all subjects through 12 months after the randomization of the last subject ~~or when 66 events (relapse as defined for the primary efficacy endpoint) have been observed, whichever is later~~. All subjects and study site personnel will remain blinded to original treatment assignment until after the final database is locked and the results of the study are made publicly available.

~~For the analysis of the primary and the major secondary efficacy endpoint, a step-down sequential testing procedure will be used to control the overall type 1 error. With this~~

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~~procedure, the primary endpoint (time to the first relapse) will be evaluated first. If the primary efficacy endpoint demonstrates statistical significance (2-sided, alpha=0.05) then inference will proceed to the major secondary efficacy endpoint, time to the first major relapse (2-sided, alpha = 0.05). If the result is statistically significant, superiority of belimumab on the time to the first major relapse will be established. If statistical significance is not met,~~ p values may be reported and considered descriptive.

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

Change to:

The database will be locked for the primary analysis after all data have been collected, verified and validated for all subjects through 12 months after the randomization of the last subject. All subjects and study site personnel will remain blinded to original treatment assignment until after the final database is locked and the results of the study are made publicly available.

Analysis of primary and secondary endpoints will be exploratory in nature. Nominal p values may be reported and considered descriptive. **Where appropriate point estimates and 95% confidence intervals will be constructed.**

Section 8.2 Randomization Procedure and Assignment to Treatment Groups

Change from:

This is a ~~Phase 3,~~ multi-center, multinational, randomized, double-blind, placebo-controlled study. Once subjects have consented, have undergone all screening procedures and have been determined to be eligible for the study, they will be randomly assigned (via an interactive web response system [IWRS]) to 1 of 2 treatment groups (belimumab [10 mg/kg] or placebo) in a 1:1 ratio. At randomization, subjects will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. RTX). Randomization will be performed on Day 0. ~~Day 0 (first administration of belimumab/placebo and azathioprine) must occur no more than 2 weeks after confirmation of remission.~~

Change to:

This is a, multi-center, multinational, randomized, double-blind, placebo-controlled study. Once subjects have consented, have undergone all screening procedures and have been determined to be eligible for the study, they will be randomly assigned (via an interactive web response system [IWRS]) to 1 of 2 treatment groups (belimumab [10 mg/kg] or placebo) in a

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1:1 ratio. At randomization, subjects will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. RTX). Randomization will be performed on Day 0.

Section 8.5.2 Primary Efficacy Analysis

Change from:

The primary efficacy analysis will compare the time to first relapse from Day 0 between the placebo/azathioprine group and the belimumab/azathioprine combination group using a Cox proportional hazard model, adjusted for ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide). However, the adjustment of induction regimen will be changed to rituximab vs. IV and/or oral cyclophosphamide if the number of events (relapse) is less 5 in subjects using the oral or IV cyclophosphamide. For any subject who does not experience a relapse, the time to first relapse will be censored at the time of the subject's last assessment. Subjects who discontinue study agent prior to relapse/flare (as defined in primary efficacy endpoint) are to be followed per protocol for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The database will be locked and the primary efficacy analysis will be performed after ~~at least 66 subjects have experienced a relapse and at least~~ 12 months have elapsed after the last subject is randomized.

Change to:

The primary efficacy analysis will compare the time to first relapse from Day 0 between the placebo/azathioprine group and the belimumab/azathioprine combination group using a Cox proportional hazard model, adjusted for ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide). However, the adjustment of induction regimen will be changed to rituximab vs. IV and/or oral cyclophosphamide if the number of events (relapse) is less **than** 5 in subjects using the oral or IV cyclophosphamide. **If there are then still less than 5 patients with an event (relapse) in any of the levels of this or any other stratification factor then the stratification term may be removed from the model.** For any subject who does not experience a relapse, the time to first relapse will be censored at the time of the subject's last assessment. Subjects who discontinue study agent prior to relapse/flare (as defined in primary efficacy endpoint) are to be followed per protocol for inclusion in the primary efficacy analysis until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). The database will be locked and the primary efficacy analysis will be performed after 12 months have elapsed **following randomization of the last subject.**

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Deleted:

Section 8.5.2.1 Subgroup Analysis

Subgroup analysis, of the primary efficacy endpoint only, will be performed in the following subgroups:

- ANCA type (anti-PR3 vs. anti-MPO)
- Disease type (WG vs. MPA)
- Disease stage at induction (initial diagnosis vs. relapsing disease)
- Induction regimen (rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide)
- Race (white, American Indian, Asian, and black)
- Region (US/Canada, EU/Australia/Israel, Americas excluding US/Canada, and Asia)
- Age (< 65 vs. ≥ 65)
- Gender
- Duration of IV corticosteroid pulse used for induction (1 day vs > 1 day)

Section 8.5.5 Major Secondary Endpoint analysis and Other Efficacy Analyses

Change from:
The analysis of the major secondary efficacy endpoint will be performed using the same method described for the primary efficacy endpoint, but censoring subjects who receive any prohibited medication (as defined in Section 5.5.1) prior to an observation of any major BVAS item. Any censoring will be applied on the date prohibited medications are received.

Change to:

The **exploratory** analysis of the major secondary efficacy endpoint will be performed using the same method described for the primary efficacy endpoint, but censoring subjects who receive any prohibited medication (as defined in Section 5.5.1) prior to an observation of any major BVAS item. Any censoring will be applied on the date prohibited medications are received.

References

Added:
Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, Study Overview and Patient Population

Change from:

This is a ~~Phase 3,~~ multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

Change to:

This is a multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen.

Change from:

~~A target of 300 to 400 subjects~~ who are between 6 and 26 weeks from starting induction therapy, achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving ≤10 mg/day prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart will be enrolled into the study.

Change to:

Approximately 100 subjects with ANCA-vasculitis who are between 6 and 26 weeks from starting induction therapy, **who** achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving ≤10 mg/day prednisone (or equivalent) on 2 consecutive measurements at least 14 days apart will be enrolled into the study.

Change from:

The database will be locked and the primary analysis will be performed ~~after at least 66 subjects have experienced a relapse and at least~~ 12 months have elapsed after the last subject is randomized.

Change to:

The database will be locked and the primary analysis will be performed **when** 12 months have elapsed after the last subject is randomized.

Deleted:

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If top-line data from the double-blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in a 6-month open-label extension period, in which all subjects will receive 10 mg/kg belimumab IV. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety.

Deleted:

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

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

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, Safety Considerations

Change from:

Per protocol, subjects are to remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase and the open-label extension.

Change to:

Per protocol, subjects are to remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase.

Appendix 13 Algorithm for Liver Chemistry Stopping and Follow-up Criteria

Added:

Liver Stopping Event Algorithm

Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.5.2.1.

References

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

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

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

> ➢ **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**

Continue Study Treatment   and   Monitor Liver Chemistry

ALT ≥5xULN
↓ Yes
ALT≥5xULN but <8xULN + bili <2xULN + no symptoms
→ Yes →
Able to monitor weekly for ≥2 weeks (Yes → above; No → below)
→ Yes →
Persists for ≥2 weeks or other stopping criteria met (No → above; Yes → below)
→ No →

ALT <5xULN
↓ Yes
ALT ≥3xULN but <5xULN + bili <2xULN + no symptoms
→ Yes →
Able to monitor weekly for ≥4 weeks (Yes → above; No → below)
→ Yes →
Persists for ≥4 weeks or other stopping criteria met (No → above; Yes → below)

Discontinue Study Treatment

> ➢ **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
>
> ➢ **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*
>
> *INR value not applicable to subjects on anticoagulants

Liver Safety Required Actions and Follow up Assessments Section can be found in Section 6.5.2.1.

Deleted:

Phase III-IV Liver Safety Algorithms

- ALT≥3xULN
  - Yes → plus bilirubin ≥2x ULN (>35% direct) (or **plus** INR >1.5, if measured)*
    - No → Hepatitis symptoms or rash?
      - No → ALT ≥8xULN
        - No → ALT ≥5xULN but <8xULN
          - Yes → Able to monitor weekly for ≥ 2 wks?
            - Yes → ALT ≥5 and <8xULN for ≥ 2 wks
              - No → ALT≥3xULN but <5xULN + bilirubin <2xULN+no symptoms
                - Yes → Able to monitor weekly for 4 weeks?
                  - Yes → Notify GSK within 24h to discuss subject safety; continue IP; check liver chemistry weekly for 4 weeks
                    - Yes → ALT<3xULN + bilirubin <2xULN after ≤ 4 wks?
                      - Yes → Continue IP Obtain twice monthly liver chemistries until normalised or back to baseline values

Left box (Yes paths):
- •Instruct subject to stop investigational product (IP)
- •Notify GSK and arrange clinical followup <u>within 24h</u>
- •Perform liver chemistries and <u>liver event follow up assessments</u> (serology, PK sample etc as in protocol)
- •<u>Report as SAE</u> (excl. hepatic impairment or cirrhosis studies) and complete liver event CRF, SAE data collection tool, and liver imaging and/or biopsy CRFs if tests performed.
- •Obtain twice weekly liver chemistries until resolved, stabilised or returned to baseline values
- •Consultation with hepatologist/specialist recommended
- •Withdraw subject from study after monitoring complete unless protocol has option to restart drug

Right box (No paths):
- •Instruct subject to stop investigational product (IP)
- •Notify GSK within 24h and arrange clinical followup within <u>24-72h</u>
- •Perform liver chemistries and <u>liver event follow up assessments</u> (serology, PK sample etc as in protocol)
- •Complete liver event CRF, SAE data collection tool if appropriate, and liver imaging and/or biopsy CRFs if tests performed.
- •Obtain weekly liver chemistries [**as far as possible in these subjects] until resolved, stabilised or returned to baseline
- •Withdraw subject from study after monitoring complete unless protocol has option to restart drug

*INR value not applicable to subjects on anticoagulants

Protocol Amendment 03 With Local Addenda 01, 02 for Ireland, 25 February 2014
Protocol Number: HGS1006-C1100

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The protocol has been modified to provide flexibility in timing of initiation of azathioprine maintenance therapy i.e., option to initiate as soon as clinically indicated and prior to confirmation of remission.
2. The protocol has been modified to allow alternative unlicensed rituximab dose for induction (1 g every 2 weeks) in addition to the licensed dosing regimen (375 mg/m^2/wk for 4 doses).
3. The protocol has been modified to provide flexibility in timing of baseline BVAS assessments – allowing 2 baseline assessments separated by at least 14 days (instead of strict 21-35 days separation).
4. The absolute requirement to randomize within 14 days of confirmation of remission has been removed and clarification has been added that subjects cannot be randomized until at least 6 weeks after initiation of induction therapy.
5. A study schematic diagram has been added to clarify the trial design.
6. Clarification has been added regarding 'high dose corticosteroids' for induction and text provides guidance but allows locally accepted practice. No subject should receive <10mg for induction.
7. The protocol has been modified to allow some flexibility to cyclophosphamide dosing regimens (allows adjustment for age, obesity, renal insufficiency, leukopenia, other toxicities) for induction.
8. The protocol has been modified to allow the option to use methotrexate from the outset, as an alternative to azathioprine, if patient is a priori known to be azathioprine intolerant or has low/absent thiopurine methyltransferase (TPMT) activity. Exclusion of subject with intolerance or contraindications to methotrexate (where this is being considered as an alternative to azathioprine).
9. The protocol has been modified to allow equal to/less than 10 mg prednisone daily during maintenance (rather than strictly <10 mg prednisone daily); articulated option to taper as clinically appropriate.
10. Progressive multifocal leukoencephalopathy text has been updated based on new information. This addition is to ensure full awareness of PML risk in the trial population and to provide clarification on clinical assessment and actions.
11. In Appendices 1 and 2, "criteria" in the title and text has been changed to "definition". The List of Appendices has been updated accordingly.
12. Appendix 5 has been updated to include a sample of the VDI case report form.

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13. The Benefit and Risk Assessment section has been updated to reflect new and/or amended information in the protocol body.

14. Minor administrative change was made for bulleted presentation in Benefit and Risk Assessment and to correct a protocol section cross-reference. These minor changes are not shown in the Modifications section below.

15. The list of abbreviations has been updated to add abbreviations as a result of new and/or amended text and to correct previous errors.

16. The date of Local Addendum 01 for Ireland has been added to the cover page for clarity.

Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment: 0~~2~~
Date: ~~27 May 2013~~
EudraCT 2011-004569-33
Local Addendum 02 for Ireland, Date: 07 August 2013

Modified to:

Protocol Amendment 0**3**
Date: **25 February 2014**
EudraCT 2011-004569-33
Local Addendum 01 for Ireland, Date: 31 January 2013
Local Addendum 02 for Ireland, Date: 07 August 2013

Revision Chronology for HGS1006-C1100 (BEL115466)

Added row:

	Date	**Document***
Global DNG2013N167980_01	**04 February 2014**	**Amendment No 03**
Local DNG2013N160488_03	**25 February 2014**	**Amendment No 03 with Local Addenda 01, 02 for Ireland**

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Synopsis, Diagnosis & Inclusion Criteria
Section 4.1, Inclusion Criteria

Formerly:
3. In the 26 weeks prior to randomization (Day 0), had an episode of moderately to severely active WG or MPA requiring treatment under one of the following induction regimens:

- A single course of rituximab administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- cyclophosphamide 2 mg/kg/day orally plus HDCS OR
- cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

5. Have a Birmingham Vasculitis Activity Score (BVAS v.3 [Appendix 3]) of 0 and be receiving ≤ 10 mg/day oral prednisone (or equivalent) on 2 consecutive measurements ~~21 to 35~~ days apart, ~~achieved no more than~~ 26 weeks after the first dose of induction therapy (either CYC or RTX, as defined in Section 3.1). ~~Maintenance therapy (belimumab/placebo + azathioprine) must start no more than 2 weeks after confirmation of remission~~.

Modified to:

3. In the 26 weeks prior to randomization (Day 0), had an episode of moderately to severely active WG or MPA requiring treatment under one of the following induction regimens:

- A single course of rituximab administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- **A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR**
- cyclophosphamide 2 mg/kg/day orally plus HDCS OR
- cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

5. Have a Birmingham Vasculitis Activity Score (BVAS v.3 [Appendix 3]) of 0 and be receiving ≤ 10 mg/day oral prednisone (or equivalent) on 2 consecutive measurements **at least 14** days apart, **between 6 and** 26 weeks after the first dose of induction therapy (either CYC or RTX, as defined in Section 3.1). **A minimum 6 week period should elapse between initiation of induction therapy and randomization.**

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Synopsis, Exclusion Criteria and Section 4.2, Exclusion Criteria

Formerly:

2. Known intolerance to azathioprine (AZA) ~~or in whom AZA is contraindicated~~.

Modified to:

2. Known intolerance **or contraindications** to azathioprine (AZA); **and known intolerance or contraindications to methotrexate where methotrexate is being considered as an alternative to AZA for maintenance therapy.**

Synopsis, Section Study Design and Schedule and Section 3.1 Basic Design Characteristics

Formerly:

Subjects enrolled into the trial must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either cyclophosphamide (CYC) or rituximab (ie, induction therapy) in the 6 months leading up to randomization. Subjects treated under the following induction regimens will be eligible for participation in the study:

*   A single course rituximab (RTX) administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
*   Cyclophosphamide 2mg/kg/day orally plus HDCS OR
*   Cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The ~~doses of~~ cyclophosphamide are ~~given~~ as targets but may be adjusted for renal insufficiency or ~~white cell counts~~ as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach <~~10~~ mg/day.

Subjects who are ~~within~~ 26 weeks of starting induction therapy, achieve a BVAS v.3 score of 0 (Appendix 4), and are receiving <~~10~~ mg/day prednisone (or equivalent) on 2 consecutive measurements ~~21 to 35~~ days apart may be enrolled into the study. Randomization will be performed on Day 0. ~~Day 0 (first administration of belimumab/placebo) must occur no more than 2 weeks after confirmation of remission. Azathioprine must be initiated at any time following confirmation of remission up to and including Day 0.~~ All subjects ~~will~~ be treated

with oral azathioprine (AZA) at a dose of 2 mg/kg/day. Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). Belimumab or placebo will be supplied by the sponsor during this double-blind treatment phase. It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, 28, and every 28 days thereafter.

Modified to:

Subjects enrolled into the trial must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either cyclophosphamide (CYC) or rituximab (ie, induction therapy) in the 6 months leading up to randomization. Subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course rituximab (RTX) administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- **A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR**
- Cyclophosphamide 2mg/kg/day orally plus HDCS OR
- Cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

*[The cyclophosphamide **dosing regimens** are **provided** as targets but may be adjusted for **older age, obesity,** renal insufficiency, **leukopenia, or other toxicities** as dictated by local practice.]*

For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by **0.5-**1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ≤ **10** mg/day. **As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.**

Subjects who are **between 6 and** 26 weeks of starting induction therapy, achieve a BVAS v.3 score of 0 (Appendix 4), and are receiving ≤ **10** mg/day prednisone (or equivalent) on 2 consecutive measurements **at least 14** days apart may be enrolled into the study. **A minimum 6 week period should elapse between initiation of induction therapy and randomization.** Randomization will be performed on Day 0. **A schematic of the study design is shown below/in Figure 1.**

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All **randomized** subjects **should** be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. **Azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine should not be initiated any later than Day 0.** Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). Belimumab or placebo will be supplied by the sponsor during this double-blind treatment phase. It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, 28, and every 28 days thereafter.

Added:

Schematic of Study Design/Figure 1 Schematic of Study Design

Section List of Abbreviations

Formerly:

CRO   Contract ~~Reseach~~ Organization
WG   Wegener's Granulmatosis

Modified to:

CRO   Contract **Research** Organization
WG   Wegener's Granulmatosis **(Granulomatosis with polyangiitis)**

Added:

TPMT   thiopurine methyltransferase

Section 1.1 Disease Background, 2nd sentence

Formerly:

A subset of the primary small vessel vasculitides: Wegener's granulomatosis; also **known** as granulomatosis with polyangiitis (GPA), microscopic polyangiitis and Churg-Strauss syndrome (CSS), are characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) (Jennette and Falk, 1997).

Modified to:

A subset of the primary small vessel vasculitides: Wegener's granulomatosis **(**also **commonly referred to** as granulomatosis with polyangiitis **[**GPA**]**), microscopic polyangiitis and Churg-Strauss syndrome (CSS), are characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) (Jennette and Falk, 1997).

Section 5.5.1 Prohibited Medications and Therapies that Result in Treatment Failure

Formerly:

- Corticosteroids for vasculitis:
  - doses > 20 mg/day prednisone (or equivalent) at any time during the study, or
  - IV corticosteroid pulses at any dose;
  Note: Doses of prednisone up to a maximum of 20 mg/day (or equivalent) for vasculitis, for a maximum of 7 days (consecutive or non consecutive), are only allowable within the first 2 months of the double-blind treatment period.

Modified to:

- Corticosteroids for vasculitis:
  - doses > 20 mg/day prednisone (or equivalent) at any time during the study, or
  - IV corticosteroid pulses at any dose;

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Note: Doses of prednisone up to a maximum of 20 mg/day (or equivalent) for vasculitis, for a maximum of 7 days (consecutive or non consecutive), are only allowable within the first 2 months of the double-blind treatment period.

Section 5.5.3 Allowable Medications

Formerly:

The use of stable baseline dose regimens of corticosteroids (~~< 10~~ mg/day prednisone or equivalent) is permitted over the course of the trial. Doses of corticosteroid up to a maximum of 20 mg/day of prednisone (or equivalent), for vasculitis, are permitted for a maximum of 7 days (consecutive or non consecutive) within the first 2 months of the double-blind treatment period. At other times, subjects are restricted to ~~< 10 mg/day~~. Inhaled corticosteroids for asthma, or topical corticosteroids for atopic dermatitis are also permitted. Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or an IV corticosteroid pulse up to 125 mg prednisone (or equivalent) are permitted for reasons other than vasculitis (eg. acute allergic reaction), but a subject cannot receive more than 1 such corticosteroid regimen in any 365 day period (See also Section 5.5.1).

Modified to:

The use of stable baseline dose regimens of corticosteroids (**≤ 10** mg/day prednisone or equivalent) is permitted over the course of the trial. Doses of corticosteroid up to a maximum of 20 mg/day of prednisone (or equivalent), for vasculitis, are permitted for a maximum of 7 days (consecutive or non consecutive) within the first 2 months of the double-blind treatment period. At other times, subjects are restricted to **≤ 10** mg/day **prednisone or equivalent. It is expected that this dose may be tapered as clinically appropriate**. Inhaled corticosteroids for asthma, or topical corticosteroids for atopic dermatitis are also permitted. Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or an IV corticosteroid pulse up to 125 mg prednisone (or equivalent) are permitted for reasons other than vasculitis (eg. acute allergic reaction), but a subject cannot receive more than 1 such corticosteroid regimen in any 365 day period (See also Section 5.5.1).

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Section 5.5.3.1 Azathioprine and Methotrexate

Formerly:

The target dose of azathioprine is 2 mg/kg/day (not to exceed 200 mg/day). Azathioprine ~~must be initiated at any time following confirmation of remission up to and including Day 0~~ at a dose of 50 mg/day and increased by no more than 50 mg/day every week until the target dose is achieved.

Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. These subjects will be included in the primary analysis.

~~It is recommended that~~ the appropriate local prescribing information (eg, contraindications, hematological and biochemical monitoring, pregnancy, contraception, etc.) for azathioprine or methotrexate (MTX) (as applicable), should be followed prior to and during treatment.

In the extension phase of the trial, the dose of AZA/MTX can be decreased or discontinued based on the discretion of the investigator.

Modified to:

The target dose of azathioprine is 2 mg/kg/day (not to exceed 200 mg/day). **For the maintenance of remission** azathioprine **may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine must not be initiated any later than Day 0. Azathioprine should be started** at a dose of 50 mg/day and increased by no more than 50 mg/day every week until the target dose is achieved.

Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. These subjects will be included in the primary analysis.

For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset. This should be discussed

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with the medical monitor. Methotrexate would not be recommended for those subjects with significantly impaired renal function.

*The appropriate local prescribing information (eg, **dose adjustments,** contraindications, hematological and biochemical monitoring, pregnancy, contraception, etc.) for azathioprine or methotrexate (MTX) (as applicable), should be followed prior to and during treatment.*

As per the Summary of Product Characteristics (SmPC) for azathioprine, it is suggested that during the first 8 weeks of therapy, complete blood counts, including platelets, should be performed weekly or more frequently if high dosage is used or if severe renal and/or hepatic disorder is present. The blood count frequency may be reduced later in therapy, but it is suggested that complete blood counts are repeated monthly, or at least at intervals of not longer than 3 months.

In the extension phase of the trial, the dose of AZA/MTX can be decreased or discontinued based on the discretion of the investigator.

Section 6.2 Study Enrollment Procedures

Formerly:

Subjects who have undergone all screening procedures and have met the entry criteria will be enrolled into the study and assigned to treatment by Interactive Web Response System (IWRS). Randomization will be performed on Day 0. ~~Day 0 (first administration of belimumab/placebo) must occur no more than 2 weeks after confirmation of remission. Azathioprine must be initiated at any time following confirmation of remission up to and including Day 0.~~ Female subjects who require pregnancy testing must have a negative urine pregnancy test done on Day 0, prior to randomization. Subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups (belimumab + AZA or placebo + AZA).

Modified to:

Subjects who have undergone all screening procedures and have met the entry criteria will be enrolled into the study and assigned to treatment by Interactive Web Response System (IWRS). Randomization will be performed on Day 0. **Azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine must not be initiated any later than Day 0.** Female subjects who require pregnancy testing must have a negative urine pregnancy test done on Day 0, prior to randomization. Subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups (belimumab + AZA or placebo + AZA).

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Table 6-1 Study Calendar, Double-blind Treatment Phase Year One Footnotes

Formerly:

10. Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1mg/kg/day. If the patient continues to experience the toxicities described above a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted.

Modified to:

10. Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1mg/kg/day. If the patient continues to experience the toxicities described above a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. **For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset following discussion with the medical monitor.**

Section 7.1 Definitions

Formerly:

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. (ICH guidelines, March 1995)

Modified to:

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above **(eg, possible drug-induced liver injury)**. These should also usually be considered serious. (ICH guidelines, March 1995)

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Section7.5 Progressive Multifocal Leukoencephalopathy

Formerly:

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

Modified to:

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. A diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The subject should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.

If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

Section 11 References

Added:

Jones,RB, Ferraro,AJ, Chaudhry,AN, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2009; 60: 2156-68.

Appendix 1 Chapel Hill Consensus Criteria for Wegener's Granulomatosis

Formerly:

Appendix 1 Chapel Hill Consensus ~~Criteria~~ for Granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) (Jennette et al, 2013)

The CHCC ~~Criteria~~ require:

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Modified to:

Appendix 1 Chapel Hill Consensus **Definition** for Granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) (Jennette et al, 2013)

The CHCC **Definition** require**s**:

Appendix 2 Chapel Hill Consensus Criteria for Microscopic Polyangiitis

Formerly:

Appendix 2 Chapel Hill Consensus ~~Criteria~~ for Microscopic Polyangiitis (MPA) (Jennette et al, 2013)

The CHCC ~~criteria~~ require:

Modified to:

Appendix 2 Chapel Hill Consensus **Definition** for Microscopic Polyangiitis (MPA) (Jennette et al, 2013)

The CHCC **Definition** require**s**:

Appendix 5 Vasculitis Damage Index

Added:

	CONFIDENTIAL		
gsk GlaxoSmithKline	**Protocol Identifier**	**BEL115466**	Final - 16 JUL 13

VASCULITIS DAMAGE INDEX (VDI)
INVESTIGATOR INSTRUCTIONS

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

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Protocol Identifier	Subject Identifier	Date of Assessment			Visit Description ✓ one:		
		Day	Month	Year			
BEL115466					☐ Screening ☐ Day 0	☐ Year____ ☐ Week 12 ☐ Week 24 ☐ Week 36 ☐ Week 48 ☐ Exit	☐ OL Day 0 ☐ OL Week 24 ☐ OL Week 28/Exit

VASCULITIS DAMAGE INDEX (VDI)

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

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Appendix 12 Protocol Addendum – Benefit and Risk Assessment, IV Belimumab

Added:

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in patients with SLE receiving immunosuppressant pharmacotherapy, including belimumab. Although the benefit-risk profile for belimumab remains unchanged following these events, the Sponsor considers that knowledge of these cases is important and has updated the clinical investigator's brochure (IB) for belimumab and revised the informed consent form (ICF) to communicate that development of PML is a potential risk.

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, Belimumab in ANCA-Associated Vasculitis, Study Overview and Patient Population

Formerly:

This is a Phase 3, multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen. Subjects enrolled into the study must have a clinical diagnosis of WG or MPA according to the Chapel Hill criteria and must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either CYC or RTX in the 6 months leading up to randomization. Subjects treated with 1 of the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- CYC 2 mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The ~~doses of CYC~~ are ~~given~~ as targets but may be adjusted for renal insufficiency or ~~white cell counts~~ as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach <~~10~~ mg/day.

A target of 300 to 400 subjects ~~who are within~~ 26 weeks ~~of~~ starting induction therapy, achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving ~~less than~~ 10 mg/day prednisone (or equivalent) on 2 consecutive measurements ~~21 to 35~~ days apart will be enrolled into the study. Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter. Randomization will be performed on Day 0. ~~Day 0 (first administration of belimumab/placebo) must occur no more than 2 weeks after confirmation of remission.~~

All subjects (in both the belimumab and placebo groups) will be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. Azathioprine must be initiated ~~at any time following confirmation of remission up to and including Day 0. Patients with known intolerance to azathioprine will be excluded from the trial.~~ Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above, a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis.

Modified to:

This is a Phase 3, multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen. Subjects enrolled into the study must have a clinical diagnosis of WG or MPA according to the Chapel Hill criteria and must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either CYC or RTX in the 6 months leading up to randomization. Subjects treated with 1 of the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- **A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR**
- CYC 2 mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

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Summary of Modifications

[*The **cyclophosphamide dosing regimens** are **provided** as targets but may be adjusted for **older age, obesity,** renal insufficiency, **leukopenia,** or **other toxicities** as dictated by local practice.*]

For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by **0.5-**1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach **≤ 10** mg/day. **As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.**

A target of 300 to 400 subjects who are **between 6 and** 26 weeks **from** starting induction therapy, achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving **≤10** mg/day prednisone (or equivalent) on 2 consecutive measurements **at least 14** days apart will be enrolled into the study. Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter. Randomization will be performed on Day 0.

All subjects (in both the belimumab and placebo groups) will be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. **For the maintenance of remission, azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy. Azathioprine must not be initiated any later than Day 0. For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset.** Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above, a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis.

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, Dose and Schedule, Induction and Maintenance Regimens for ANCA-Associated Vasculitis

Formerly:

Subjects participating in this trial will have had a moderate to severe episode of WG or MPA that was treated with high-dose corticosteroids (HDCS) and either RTX or CYC (IV or oral) to induce the remission of the disease. Subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- CYC 2mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The ~~doses of~~ cyclophosphamide are ~~given~~ as targets but may be adjusted for renal insufficiency or ~~white cell counts~~ as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ~~< 10~~ mg/day.

Rituximab was approved in April 2011 by the FDA for the treatment of WG and MPA. It has been used in induction of remission in AAV for a number of years, (Gorman et al, 2003, Smith et al, 2006) and 2 recent trials published in 2010 (Stone et al, 2010), demonstrated non-inferiority to induction with cyclophosphamide, the latter of these trials being used as the basis for the recent US approval. The RTX ~~regimen specified in this vasculitis study is the same~~ as that approved by the FDA for this indication.

Cyclophosphamide (2 mg/kg/day orally or IV 15 mg every 2 weeks for 3 doses and every 3 weeks thereafter) plus prednisone has been the standard induction regimen for WG and MPA since the early 1970s when initial work by Fauci and Wolff at the National Institutes of Health showed that this regimen induced disease remission in 12/14 patients and subsequent work showed that survival rates increased 80% using this regimen in what was previously an uniformly fatal disease (Fauci and Wolff, 1973; Fauci et al, 1983; Hoffman et al, 1992; Langford, 2011). Long term continued cyclophosphamide use, however, has been associated with significant toxicities (including infection, cystitis, cytopenias, and long term complications such as myelodysplasia and bladder cancer) and mortality (Langford, 2011).

A more recent study conducted by the European Vasculitis Group (Jayne et al, 2003) showed that after initial disease remission with cyclophosphamide and steroids, subjects could be switched to azathioprine (2 mg/kg/day) without having an increased risk of relapse compared to subjects whose remission was maintained using continued cyclophosphamide treatment. An induction regimen of CYC + prednisone followed by maintenance treatment with azathioprine

is now considered the standard of care, given that administration of cyclophosphamide for longer durations does not offer an advantage from an efficacy standpoint and is associated with a greater potential for toxicity (Langford, 2011). The cyclophosphamide regimens described above are the same as those allowed in the inclusion criteria for this vasculitis study.

Once disease remission (defined as having, on 2 consecutive measurements ~~3 to 5~~ weeks apart: a BVAS v3 score of 0 and be receiving ~~< 10~~ mg/day of oral prednisone [or equivalent], ~~no more than~~ 26 weeks after the first dose of induction therapy) has been achieved, subject randomization into this protocol occurs. In this maintenance of remission trial, subjects will be randomized to receive a maintenance regimen of AZA (2 mg/kg/day) + placebo or AZA (2 mg/kg/day) + belimumab (10 mg/kg). Randomization in this protocol ~~must occur within 2 weeks of achieving a confirmed remission and the randomization~~ will be stratified by induction regimen.

The primary safety population for the SLE indication, including 473 subjects who were taking azathioprine as a concomitant medication at baseline, provides a substantial amount of safety data to support the conduct of the proposed trial. ~~In this study, subjects who have a known intolerance to azathioprine will be excluded.~~ Subjects naive to azathioprine and who experience azathioprine-related toxicity (Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT 2 times ULN, or a several gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting), following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience toxicities, a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis. The protocol instructs physicians to follow the appropriate local prescribing information for azathioprine or methotrexate (as applicable) prior to and during treatment.

Input on selection of these standard of care regimens was obtained from international experts in vasculitis, including members of the European Vasculitis Society (EUVAS) and the Vasculitis Clinical Research Consortium (VCRC), and consensus was reached that these regimens are appropriate for this international trial.

Complete details regarding the use of concurrent medications can be found in Section 5.5 of Protocol HGS1006-C1100.

Modified to:

Subjects participating in this trial will have had a moderate to severe episode of WG or MPA that was treated with high-dose corticosteroids (HDCS) and either RTX or CYC (IV or oral) to induce the remission of the disease. Subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- **A single course of rituximab comprising two doses, 1g IV each, separated by a two-week interval, plus HDCS OR**
- CYC 2mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

*[The cyclophosphamide **dosing regimens** are **provided** as targets but may be adjusted for **older age, obesity,** renal insufficiency, **leukopenia,** or **other toxicities** as dictated by local practice.]*

For guidance purposes, the recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 0.5-1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach ≤ **10** mg/day. **As doses for HDCS pulses per the protocol are recommended doses, local standard of care for the steroid dosing regimen would be acceptable if intravenous steroid pulses are not part of standard of care on site. However, all subjects must be receiving more than 10 mg of prednisone/day or equivalent for induction.**

Rituximab was approved in April 2011 by the FDA for the treatment of WG and MPA. It has been used in induction of remission in AAV for a number of years, (Gorman et al, 2003, Smith et al, 2006) and 2 recent trials published in 2010 (Stone et al, 2010), demonstrated non-inferiority to induction with cyclophosphamide, the latter of these trials being used as the basis for the recent US approval. The RTX **dosing regimen of 4 infusions of 375 mg/m^2 each given 1 week apart reflects the dosing regimen** that **is** approved by the FDA for this indication. **An alternative RTX induction regimen (2 infusions of 1 gram each administered 2 weeks apart) is also offered in the protocol. Although the latter regimen is not licensed as an induction therapy for ANCA-vasculitis, it is very widely used in clinical practice and clinical evidence suggests that there is no difference between the two dosing regimens in terms of duration of B-cell depletion or therapeutic efficacy efficacy (Jones et al, 2009).**

Cyclophosphamide (2 mg/kg/day orally or IV 15 mg every 2 weeks for 3 doses and every 3 weeks thereafter) plus prednisone has been the standard induction regimen for WG and MPA since the early 1970s when initial work by Fauci and Wolff at the National Institutes of Health showed that this regimen induced disease remission in 12/14 patients and subsequent work showed that survival rates increased 80% using this regimen in what was previously an uniformly fatal disease (Fauci and Wolff, 1973; Fauci et al, 1983; Hoffman et al, 1992; Langford, 2011). Long term continued cyclophosphamide use, however, has been associated with significant toxicities (including infection, cystitis, cytopenias, and long term complications such as myelodysplasia and bladder cancer) and mortality (Langford, 2011).

A more recent study conducted by the European Vasculitis Group (Jayne et al, 2003) showed that after initial disease remission with cyclophosphamide and steroids, subjects could be switched to azathioprine (2 mg/kg/day) without having an increased risk of relapse compared to subjects whose remission was maintained using continued cyclophosphamide treatment. An induction regimen of CYC + prednisone followed by maintenance treatment with azathioprine is now considered the standard of care, given that administration of cyclophosphamide for longer durations does not offer an advantage from an efficacy standpoint and is associated with a greater potential for toxicity (Langford, 2011). The cyclophosphamide regimens described above are the same as those allowed in the inclusion criteria for this vasculitis study.

Once disease remission (defined as having, on 2 consecutive measurements **at least 14 days** apart: a BVAS v3 score of 0 and be receiving ≤ **10** mg/day of oral prednisone [or equivalent], **between 6 and** 26 weeks after the first dose of induction therapy) has been achieved, subject randomization into this protocol occurs. In this maintenance of remission trial, subjects will be randomized to receive a maintenance regimen of AZA (2 mg/kg/day) + placebo or AZA (2 mg/kg/day) + belimumab (10 mg/kg). Randomization in this protocol will be stratified by induction regimen.

The primary safety population for the SLE indication, including 473 subjects who were taking azathioprine as a concomitant medication at baseline, provides a substantial amount of safety data to support the conduct of the proposed trial. **For the maintenance of remission, azathioprine may be initiated as soon as it is clinically indicated following administration of induction therapy and no later than Day 0. For subjects previously identified as being intolerant to azathioprine, or for subjects identified as having undetectable or reduced activity of thiopurine methyltransferase (TPMT), it may be permissible for methotrexate to be used as an alternative to azathioprine for the maintenance of remission from the outset.** Subjects naive to azathioprine and who experience azathioprine-related toxicity (Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT 2 times ULN, or a several gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting), following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience toxicities, a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis. The protocol instructs physicians to follow the appropriate local prescribing information for azathioprine or methotrexate (as applicable) prior to and during treatment.

Input on selection of these standard of care regimens was obtained from international experts in vasculitis, including members of the European Vasculitis Society (EUVAS) and the Vasculitis Clinical Research Consortium (VCRC), and consensus was reached that these regimens are appropriate for this international trial.

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Summary of Modifications

Complete details regarding the use of concurrent medications can be found in Section 5.5 of Protocol HGS1006-C1100.

Appendix 12 Protocol Addendum – Benefit and Risk Assessment, Safety Considerations

Added:

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in patients with SLE receiving immunosuppressant pharmacotherapy, including belimumab. Therefore, a diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The protocol requires that subjects should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy. If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

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Protocol HGS1006-C1100-02 Addendum 02 (Ireland) Summary of Modifications   Belimumab

Protocol Amendment 02 with Local Addendum 02 for Ireland, 07 August 2013
Protocol Number: HGS1006-C1100

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The protocol has been modified, at the request of the Irish Medicines Board, to further clarify the timing of restrictions regarding steroid use for vasculitis.

Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment: 02
Date: 27 May 2013
Local Addendum 01 for Ireland, Date: 31 January 2013

Modified to:

Protocol Amendment: 02
Date: 27 May 2013
Local Addendum 02 for Ireland, Date: 07 August 2013

Section 5.5.1 Prohibited Medications and Therapies that Result in Treatment Failure

Formerly:

- Corticosteroids for vasculitis:
  doses > 20 mg/day prednisone (or equivalent) for > 1 week, or
  IV corticosteroid pulses at any dose;
  Note: Doses of prednisone up to a maximum of 20 mg/day (or equivalent) for vasculitis, for a maximum of 1 week, are only allowable within the first 2 months of the double-blind treatment period.

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Modified to:

- Corticosteroids for vasculitis:
  doses > 20 mg/day prednisone (or equivalent) **at any time during the study**, or
  IV corticosteroid pulses at any dose;
  Note: Doses of prednisone up to a maximum of 20 mg/day (or equivalent) for vasculitis,
  for a maximum of **7 days (consecutive or non consecutive)**, are only allowable within the
  first 2 months of the double-blind treatment period.

Section 5.5.3 Allowable Medications

Formerly:

The use of stable baseline dose regimens of corticosteroids (< 10 mg/day prednisone or
equivalent) is permitted over the course of the trial. Doses of corticosteroid up to a maximum
of 20 mg/day of prednisone (or equivalent), for vasculitis, are permitted for a maximum of
1 week within the first 2 months of the double-blind treatment period. At other times, subjects
are restricted to < 10 mg/day. Inhaled corticosteroids for asthma, or topical corticosteroids for
atopic dermatitis are also permitted. Doses of prednisone (or equivalent) > 20mg/day for ≤ 14
days or an IV corticosteroid pulse up to 125 mg prednisone (or equivalent) are permitted for
reasons other than vasculitis (eg. acute allergic reaction), but a subject cannot receive more
than 1 such corticosteroid regimen in any 365 day period (See also Section 5.5.1).

Modified to:

The use of stable baseline dose regimens of corticosteroids (< 10 mg/day prednisone or
equivalent) is permitted over the course of the trial. Doses of corticosteroid up to a maximum
of 20 mg/day of prednisone (or equivalent), for vasculitis, are permitted for a maximum of
7 days (consecutive or non consecutive) within the first 2 months of the double-blind
treatment period. At other times, subjects are restricted to < 10 mg/day. Inhaled
corticosteroids for asthma, or topical corticosteroids for atopic dermatitis are also permitted.
Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or an IV corticosteroid pulse
up to 125 mg prednisone (or equivalent) are permitted for reasons other than vasculitis (eg.
acute allergic reaction), but a subject cannot receive more than 1 such corticosteroid regimen
in any 365 day period (See also Section 5.5.1).

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Protocol HGS1006-C1100-02 Addendum 01 (Ireland) Summary of Modifications   Belimumab

Protocol Amendment 02 with Local Addendum 01 for Ireland, 27 May 2013
Protocol Number: HGS1006-C1100

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The protocol has been modified to include testing at Screening for HIV antibody, to expand Hepatitis B serology testing, and to exclude patients who test positive according to the criteria specified.
2. Because the RIBA antibody confirmation assay for hepatitis C is not available due to non-availability of manufacturer's reagents, an alternative test, HCV RNA-PCR assay, will be used to detect the presence of viral RNA, and hence confirm a current infection.
3. The protocol has been modified to exclude patients at baseline with abnormal liver function according to the criteria specified.
4. A new section has been added to clarify how patient care should be managed if a patient has a liver chemistry event during the study. The accompanying figure has been placed in an appendix (Appendix 13) and the List of Appendices has been updated accordingly.
5. Measurement of vital signs (temperature, sitting blood pressure [systolic and diastolic], and heart rate) have been added to the procedures for all scheduled study visits and a 12-lead ECG has been added to the procedures for the Day 0 visit. These procedures have been added to provide increased understanding and to assist analyses of potential safety events should they occur.
6. A page with the protocol's revision chronology has been added.
7. The Synopsis has been corrected to include study agent dosing on day 28.
8. Text has been added to clarify that study agents (belimumab or placebo) will be provided by the sponsor during the double-blind treatment phase and that belimumab will be provided by the sponsor during the open-label extension phase.
9. Within the definition of postmenopausal in Inclusion Criterion #7, "1 year without menses" has been changed to "12 consecutive months with no menses without an alternative medical cause." Also, the sub-bullet formatting of the last 8 rows of Inclusion Criterion #7 has been corrected.
10. Steroid use for vasculitis has been modified to restrict the use of corticosteroids up to a maximum of 20 mg/day of prednisone (or equivalent) for a maximum of 1 week within the first 2 months of the double-blind treatment period, and at other times, to < 10 mg/day.
11. The Reference List has been updated to include references cited in text but not present in the list and to delete a reference included in error. Also, the in text citation for Posner et al has been corrected to Posner et al 2007 and the reference has been added to the list.
12. Cross-references have been added in Section 1 for references that were in the Reference List but which inadvertently had not been cited in text.

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13. In Appendix 8, for the question at baseline/screening "Is the time the subject felt most suicidal (i.e. the lifetime rating) more than X month(s) ago?", the "X" has been corrected to "2", i.e, "more than 2 month(s) ago".

14. The investigator evaluation of adverse events regarding causality has been modified from a multi-choice assessment (definitely related, probably related, etc.) to an assessment of "reasonable possibility".

15. Appendix 9 has been corrected to cite the reference and the publication has been added to the Reference List.

16. Two new appendices have been added to provide the questionnaires for the PSRHQ (Appendix 10) and the PSRQ (Appendix 11) and cross-references added in-text as appropriate. The List of Appendices has been updated accordingly.

17. The protocol has been modified to include a Benefit and Risk Assessment (Appendix 12). The List of Appendices has been updated accordingly.

18. Minor administrative change was made for presentation of cross-referencing sections and tables, e.g., "see Sections X.1 and X.2" was changed to "see Section X.1 and Section X.2". These minor changes are not shown in the Modifications section below.

19. The list of abbreviations has been updated to add abbreviations as a result of new and/or amended text and to correct previous errors.

20. The Chapel Hill Consensus Conference (CHCC) definitions for Wegener's granulomatosis and microscopic polyangiitis in Appendices 1 and 2 of the protocol have been updated to reflect the most recent CHCC (2012) definitions. The reference for this (Jeannette et al 2013) is cited in the text (Section 1.1) and in the reference list.

Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment: 01
Date: 22 June 2012
Local Addendum 01 for Ireland, Date: 31 January 2013

Modified to:

Protocol Amendment: **02**
Date: **27 May 2013**
Local Addendum 01 for Ireland, Date: 31 January 2013

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Revision Chronology for HGS1006-C1100 (BEL115466)

Added:

	Date	Document*
Global	07 March 2012	Original
Global	22 June 2012	Amendment No 01
Local	29 January 2013	Addendum 01 for Sweden
Local DNG2013N160488_00	31 January 2013	Addendum 01 for Ireland
Global DNG2013N167980_00	25 April 2013	Amendment No 02
Local DNG2013N160488_01	27 May 2013	Amendment No 02 with Addendum 01 for Ireland

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

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Synopsis, Diagnosis & Inclusion Criteria
Section 4.1, Inclusion Criteria

Formerly:

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

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Modified to:

7. A female subject is eligible to enter the study if she is:
   - Not pregnant or nursing;
   - Of non-childbearing potential (ie, women who had a hysterectomy, are postmenopausal which is defined as **12 consecutive months with no menses without an alternative medical cause**, have both ovaries surgically removed or have current documented tubal ligation or other permanent sterilization procedure); <u>or</u>
   - Of childbearing potential (ie, women with functional ovaries and no documented impairment of oviductal or uterine function that would cause sterility). This category includes women with oligomenorrhoea [even severe], women who are peri-menopausal or have just begun to menstruate. These women must have a negative serum pregnancy test at screening, and agree to 1 of the following:
     o Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent; <u>or</u>
     o Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:
       o Implants of levonorgestrel or etonogestrel;
       o Injectable progesterone;
       o Transdermal contraceptive patch
       o Any intrauterine device (IUD) with a documented failure rate of less than 1% per year;
       o Oral contraceptives (either combined or progesterone only);
       o Ethinyl estradiol/Etonogestrel vaginal ring
       o Double barrier method: Condom and Occlusive cap (diaphragm or cervical/vault caps) with spermidical foam/gel/film/cream/suppository; or
       o 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.

Synopsis, Exclusion Criteria and Section 4.2, Exclusion Criteria

Formerly:

12. Have a historically positive test or test positive at screening for hepatitis B surface antigen, or hepatitis C antibody or are known to be HIV-1 positive.

Modified to:

12. Have a historically positive HIV test or test positive at screening for HIV.

13. Hepatitis B: Serologic evidence of Hepatitis B (HB) infection based on the results of testing for HBsAg, anti-HBc and anti-HBs as follows:

- **Patients positive for HBsAg are excluded.**
- **Patients negative for HBsAg and anti-HBc antibody but positive for anti-HBs antibody and with no history of Hepatitis B vaccination are excluded.**
- **Patients negative for HBsAg but positive for both anti-HBc and anti-HBs antibodies are excluded.**
- **Patients negative for HBsAg and anti-HBs antibody but positive for anti-HBc antibody are excluded.**

14. **Hepatitis C: Positive test for Hepatitis C antibody confirmed on a subsequent blood sample by RNA-PCR assay. Subjects who are positive for Hepatitis C antibody and negative when the Hepatitis C RNA-PCR assay is performed on a subsequent sample will be eligible to participate. Subjects who are positive for Hepatitis C antibody and have a positive result for the HCV when the Hepatitis C RNA-PCR assay is performed on the subsequent sample will not be eligible to participate.**

Added:

19. **Subjects who have abnormal liver function tests defined as follows: 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%).**

Synopsis, Section Study Design and Schedule

Formerly:

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter.

Modified to:

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). **Belimumab or placebo will be supplied by the sponsor during this double-blind treatment phase.** It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, **28,** and every 28 days thereafter.

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Formerly:

If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months.

Modified to:

If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months **and this will be supplied by the sponsor**.

Section List of Abbreviations

Formerly:

ALT   aspartate aminotransferase alanine
LDH   lactic dehydrogenase

Modified to:

ALT   **alanine** aminotransferase
LDH   **lactate** dehydrogenase

Added:

CPK   **creatine phosphokinase**
ECG   **electrocardiogram**
HB   **hepatitis B**
HBsAg   **hepatitis B surface antigen**
HBc   **hepatitis B core**
HCV   **hepatitis C virus**

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Section 1.1 Disease Background

Formerly:

Anti-PR3 antibodies are associated with increased morbidity and mortality compared to anti-MPO. The most widely used classification criteria for diagnosing the 3 types of AAV are those published by the American College of Rheumatology (ACR) for WG and CSS (Leavitt et al, 1990 and Masi et al, 1990, respectively), and that published by the Chapel Hill Consensus Conference (CHCC) for MPA (Jennette et al, 1994).

The precise epidemiology of these diseases is uncertain as early studies did not utilize the same classification criteria as later ones (Koldingsnes and Nossent, 2008; Watts et al, 2007).

In the US, the prevalence rates of WG range from 2.6-9/100000 (Mahr et al, 2006).

Modified to:

Anti-PR3 antibodies are associated with increased morbidity and mortality compared to anti-MPO **(Hogan et al, 1996; Franssen et al, 1998)**. The most widely used classification criteria for diagnosing the 3 types of AAV are those published by the American College of Rheumatology (ACR) for WG and CSS (Leavitt et al, 1990 and Masi et al, 1990, respectively), and that published by the Chapel Hill Consensus Conference (CHCC) for MPA (Jennette et al, 1994; **Jennette et al, 2013**).

The precise epidemiology of these diseases is uncertain as early studies did not utilize the same classification criteria as later ones (Koldingsnes and Nossent, 2008; Watts et al, 2007; **Mahr, 2009**).

In the US, the prevalence rates of WG range from 2.6 9/100000 (**Zeft et al, 2005;** Mahr et al, 2006).

Section 1.3.1 Belimumab Administered Intravenously

Added:

A benefit-risk evaluation of belimumab in the context of the present study is provided in Appendix 12 of this protocol.

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Section 1.4 Rationale for the Study

Formerly:

The fact that rituximab, a biologic therapy that targets B cells by binding to the B cell surface antigen CD20, recently showed success in inducing remission in AAV (Stone et al, 2010) and was granted approval for the treatment of WG and MPA supports the rationale that belimumab, which down regulates B cells by targeting BLyS, may be useful in the treatment of this disease.

Modified to:

The fact that rituximab, a biologic therapy that targets B cells by binding to the B cell surface antigen CD20 **(Dass et al, 2008; Wang et al 2008)**, recently showed success in inducing remission in AAV (Stone et al, 2010) and was granted approval for the treatment of WG and MPA supports the rationale that belimumab, which down regulates B cells by targeting BLyS, may be useful in the treatment of this disease.

Section 3.1 Basic Design Characteristics

Formerly:

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter.

Modified to:

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease) and induction regimen (IV cyclophosphamide vs. oral cyclophosphamide vs. rituximab). **Belimumab or placebo will be supplied by the sponsor during this double-blind treatment phase.** It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Study agent (belimumab/placebo) will be administered at Day 0, 14, 28, and every 28 days thereafter.

Formerly:

If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given

the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months.

Modified to:

If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in the open-label extension phase. Subjects who enter the open-label extension phase will receive belimumab for up to an additional 6 months **and this will be supplied by the sponsor**.

Section 5.5.1 Prohibited Medications and Therapies that Result in Treatment Failure

Formerly:

- Corticosteroids for vasculitis:
  - doses > 20 mg/day prednisone (or equivalent), or
  - IV corticosteroid pulses at any dose;

Modified to:

- Corticosteroids for vasculitis:
  - doses > 20 mg/day prednisone (or equivalent) **for > 1 week**, or
  - IV corticosteroid pulses at any dose;
  Note: Doses of prednisone up to a maximum of 20 mg/day (or equivalent) for vasculitis, for a maximum of 1 week, are only allowable within the first 2 months of the double-blind treatment period.

Section 5.5.3 Allowable Medications

Formerly:

The use of stable baseline dose regimens of corticosteroids (< 10 mg/day prednisone or equivalent) is permitted over the course of the trial. Inhaled corticosteroids for asthma, or topical corticosteroids for atopic dermatitis are also permitted. Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or an IV corticosteroid pulse up to 125 mg prednisone (or equivalent) are permitted for reasons other than vasculitis (eg. acute allergic reaction), but a subject cannot receive more than 1 such corticosteroid regimen in any 365 day period (See also Section 5.5.1).

Modified to:

The use of stable baseline dose regimens of corticosteroids (< 10 mg/day prednisone or equivalent) is permitted over the course of the trial. **Doses of corticosteroid up to a maximum of 20 mg/day of prednisone (or equivalent), for vasculitis, are permitted for a maximum of 1 week within the first 2 months of the double-blind treatment period. At other times, subjects are restricted to < 10 mg/day.** Inhaled corticosteroids for asthma, or topical corticosteroids for atopic dermatitis are also permitted. Doses of prednisone (or equivalent) > 20mg/day for ≤ 14 days or an IV corticosteroid pulse up to 125 mg prednisone (or equivalent) are permitted for reasons other than vasculitis (eg. acute allergic reaction), but a subject cannot receive more than 1 such corticosteroid regimen in any 365 day period (See also Section 5.5.1).

Section 6.1 Screening Procedures (Day -60 to Day 0):

Formerly:

- Blood samples for: (see Appendix 6 – Laboratory Tests)
  - Hepatitis B surface antigen, and Hepatitis C antibody testing

Modified to:

- Blood samples for: (see Appendix 6 – Laboratory Tests)
  - **HIV antibody testing, serologic investigations for Hepatitis B (HB) infection (**HBsAg, **anti-HBc, and anti-HBs), and** Hepatitis C antibody testing ± **confirmatory HCV RNA-PCR testing**

Table 6-1 Study Calendar, Double-blind Treatment Phase Year One
Vital signs: All scheduled visits

Formerly:

Not listed.

Modified to:

Vital signs[18, 19] is added to the study calendar under Clinical Assessments.

Vital signs is marked "**X**" as required at all scheduled visits.

Table 6-1 Study Calendar, Double-blind Treatment Phase Year One
12-lead ECG: Day 0 Visit

Formerly:

Not listed.

Modified to:

12-lead ECG[19] is added to the study calendar under Clinical Assessments.

12-lead ECG is marked "**X**" as required at this visit.

Table 6-1 Study Calendar, Double-blind Treatment Phase Year One
HIV, Hepatitis B, C: Screening Visits

Formerly:

Hep B surface antigen & Hep C antibody

Modified to:

HIV, Hepatitis B, C[20]

HIV, Hepatitis B, C is marked "**X**" as required at this visit.

Table 6-1 Study Calendar, Double-blind Treatment Phase Year One
Footnotes

Formerly:

[1]Complete physical examination, including height, weight and vital signs.

Modified to:

[1]Complete physical examination, including height and weight.

A*dded:*

[18]Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate.

[19]Complete prior to dosing.

[20]HIV, Hepatitis B surface antigen, anti-HBc, anti-HBs and hepatitis C antibody (if hepatitis C antibody positive, HCV RNA-PCR assay will be performed on a subsequent blood sample to confirm the results).

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**Table 6-2 Study Calendar, Double-blind Treatment Phase Additional Years
Vital signs: All scheduled visits**

Formerly:

Not listed.

Modified to:

Vital signs[11, 12] is added to the study calendar under Clinical Assessments.

Vital signs is marked "**X**" as required at all scheduled visits.

**Table 6-2 Study Calendar, Double-blind Treatment Phase Additional Years
Footnotes**

Added

[11]Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate.

[12]Complete prior to dosing.

**Table 6-3 Study Calendar, Open-Label Extension Phase
Vital signs: All scheduled visits**

Formerly:

Not listed.

Modified to:

Vital signs[12, 13] is added to the study calendar under Clinical Assessments.

Vital signs is marked "**X**" as required at all scheduled visits.

**Table 6-3 Study Calendar, Open-Label Extension Phase
Footnotes**

Added:

[12]Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate.

[13]Complete prior to dosing.

Section 6.6 Laboratory Tests

The following section has been added:

Section 6.6.2 Phase III-IV Liver Chemistry Stopping and Follow-up Criteria

The liver chemistry stopping and follow-up criteria have been designed to assure subject safety and evaluate liver event etiology.

Phase III-IV liver chemistry stopping criteria 1-5 are defined below and presented in a figure in Appendix 13:

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

    NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug from that subject if ALT $\geq$ 3xULN and bilirubin $\geq$ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT $\geq$ 8xULN.

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

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

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

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

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

    NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug from that subject if ALT $\geq$ 3xULN **and** bilirubin $\geq$ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

*   Complete the liver imaging and/or liver biopsy CRFs if these tests are performed

- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.

- Withdraw the subject from the **study** (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
- Do not re-start investigational product.

In addition, for criterion 1:

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

For criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hours** 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 $\geq$5xULN and <8xULN which exhibit a decrease to ALT $\geq$3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety
- Can continue investigational product
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

For criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- • Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);

- Hepatitis C RNA;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Hepatitis E IgM antibody;

- Blood sample for PK analysis, obtained within approximately 1 to 2 weeks after the liver event. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Procedures Manual.
- 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, paracetamol (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 and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

Section 7.6 Suicidality Assessment

Formerly:

Subjects who answer "yes" to any suicidal behavior or "yes" to suicidal ideation questions 4 or 5 on the C-SSRS should be referred to appropriate psychiatric care and prompts the completion of an SAE worksheet. The medical monitor should be notified when these events occur. In addition, a "yes" to any suicidal behavior or "yes" to suicidal ideation question 3, 4 or 5 on the C-SSRS prompts the completion of the Possible Suicidality Related History

Questionnaire (PSRHQ, only the first time this condition is met) eCRF and a Possible Suicidality Related Questionnaire (PSRQ) eCRF (at all times this condition is met).

Baseline/Screening and during treatment assessment of suicidality will be performed during the blinded portion of this study using C-SSRS (Refer to Appendix 8 for C-SSRS). The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both behaviour and ideation (Posner et al, 2010).

Modified to:

Subjects who answer "yes" to any suicidal behavior or "yes" to suicidal ideation questions 4 or 5 on the C-SSRS should be referred to appropriate psychiatric care and prompts the completion of an SAE worksheet. The medical monitor should be notified when these events occur. In addition, a "yes" to any suicidal behavior or "yes" to suicidal ideation question 3, 4 or 5 on the C-SSRS prompts the completion of the Possible Suicidality Related History Questionnaire (PSRHQ, only the first time this condition is met**; refer to Appendix 10 for the PSRHQ**) eCRF and a Possible Suicidality Related Questionnaire (PSRQ) eCRF (at all times this condition is met**; refer to Appendix 11 for the PSRQ**).

Baseline/Screening and during treatment assessment of suicidality will be performed during the blinded portion of this study using C-SSRS (Refer to Appendix 8 for C-SSRS). The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both behaviour and ideation (Posner et al, **2007**).

Section7.6.1 Possible Suicidality Related Questionnaire (PSRQ)

Formerly:

The investigator will be prompted to complete the PSRQ (in addition to the AE or SAE pages, as appropriate) if a yes response is given to any suicidal behavior or a yes response to suicidal ideation questions 3, 4 or 5 on the C-SSRS.

Modified to:

The investigator will be prompted to complete the PSRQ (in addition to the AE or SAE pages, as appropriate) if a yes response is given to any suicidal behavior or a yes response to suicidal ideation questions 3, 4 or 5 on the C-SSRS. **Refer to Appendix 11 for the PSRQ.**

Section 7.8 Investigator Evaluation of Adverse Events

Formerly:

CAUSALITY

Definitely Related   - reasonable temporal relationship to study agent administration

	- follows a known response pattern (eg, study agent is known to cause this AE) - there is no alternative etiology
Probably Related	- reasonable temporal relationship - follows a suspected response pattern (eg, based on similar drugs) - no evidence for a more likely alternative etiology
Possibly Related	- reasonable temporal relationship - little evidence for a more likely alternative etiology
Probably Not Related	- does not have a reasonable temporal relationship OR - good evidence for a more likely alternative etiology
Not Related	- does not have a temporal relationship OR - definitely due to alternative etiology

The causality assessment must be made by the investigator based on information available at the time that the AE eCRF or SAE worksheet is completed. The initial causality assessment may be revised as new information becomes available.

Modified to:

CAUSALITY

It is a regulatory requirement for investigators to assess relationship between the investigational product(s) and the occurrence of each AE/SAE based on the information available. The assessment should be reviewed on receipt of any new information and amended if necessary. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support "a reasonable possibility" include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

Section 11 References

Formerly:

Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009; 68:1827-32.

Modified to:

Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009; 68:1827-32. **doi: 10.1136/ard.2008.101279. Epub 2008 Dec3**.

Added:

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Fauci AS, Wolff SM. Wegener's granulomatosis: studies in eighteen patients and a review of the literature. Medicine (Baltimore) 1973;52:535-61.

Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 1983;98:76-85.

Gorman C, Leandro M, Isenberg D. B cell depletion in autoimmune disease. Arthritis Res Ther 2003;5 (Suppl 4):S17-S21.

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Langford CA. Cyclophosphamide as induction therapy for Wegener's granulomatosis and microscopic polyangiitis. Clin Exp Immunol. 2011;164 (Suppl 1):31-4. doi: 10.1111/j.1365-2249.2011.04364.x.

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Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007;164:1035-43.

Smith KGC, Jones RB, Burns SM, Jayne DR. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. Arthritis Rheum 2006;54:2970-82.

Stenager EN, Stenager E, Koch-Henriksen N, et al. Suicide and multiple sclerosis: an epidemiological investigation. J Neurology, Neurosurg Psychiatry 1992;55:542-5.

Timonen M, Viilo K, Hakko H, et al. Suicides in persons suffering from rheumatoid arthritis. Rheumatology 2003;42:287-91.

Walters GD, Willis NS, Craig JC. Interventions for renal vasculitis in adults. A systematic review.BMC Nephrol 2010;11:12. doi: 10.1186/1471-2369-11-12.

Deleted:

Szczeklik W, Jakieła B, Adamek D, et al. Cutting Edge Issues in the Churg-Strauss Syndrome. Clin Rev Allergy Immunol 2011;66:222-7.

Appendix 1 Chapel Hill Consensus Criteria for Wegener's Granulomatosis

Formerly:

The CHCC Criteria require:

Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (eg, capillaries, venules, arterioles, and arteries) for a diagnosis of Wegener's.

Another symptoms that may be present in WG, but that are not required according the CHCC classification scheme, is necrotizing glomerulonephritis.

Modified to:

Appendix 1 Chapel Hill Consensus Criteria for **Granulomatosis with polyangiitis (GPA) (**Wegener's Granulomatosis**) (Jennette et al, 2013)**

The CHCC Criteria require:

Necrotizing granulomatous inflammation **usually** involving the **upper and lower** respiratory tract, and necrotizing vasculitis affecting **predominantly** small to medium-sized vessels (eg, capillaries, venules, arterioles, and arteries) for a diagnosis of Wegener's.

Another feature that may be **commonly** present in **GPA**, but **which is** not required according **to** the CHCC **definition**, is necrotizing glomerulonephritis.

Appendix 2 Chapel Hill Consensus Criteria for Microscopic Polyangiitis

Formerly:

The CHCC criteria require:

Necrotizing vasculitis with few or no immune deposits that affects small vessels (ie, capillaries, venules, or arterioles) for a diagnosis of MPA.

Other symptoms that may be present in MPA, but that are not required according the CHCC classification scheme, are: necrotizing arteritis involving small- and medium-sized vessels; glomerulonephritis; and pulmonary capilliaritis.

Modified to:

Appendix 2 Chapel Hill Consensus Criteria for Microscopic Polyangiitis **(MPA) (Jennette et al, 2013)**

The CHCC criteria require:

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Necrotizing vasculitis, with few or no immune deposits, **predominantly affecting** small vessels (ie, capillaries, venules, or arterioles) for a diagnosis of MPA. **Granulomatous inflammation is absent.**

Other **features** that may be present in MPA, but that are not required according **to** the CHCC **definition**, are: necrotizing arteritis involving small- and medium-sized **arteries**; **commonly necrotizing** glomerulonephritis; and **often** pulmonary **capillaritis**.

Appendix 6 Laboratory Tests

Formerly:

Enzymes:
    SGOT (AST)
    SGPT (ALT)
    Alkaline Phosphatase
    Gamma glutamyl transferase (GGT)
    Lactic dehydrogenase (LDH)
Other:
    Creatinine
    Blood urea nitrogen (BUN)
    BUN/creatinine ratio
    Bilirubin, total
    Protein, total
    Albumin
    Uric acid
    Glucose
    Hepatitis C antibody
    Hepatitis B surface antigen
    Estimated Creatinine Clearance/ GFR (Cockcroft-Gault)

Modified to:

Enzymes:
    SGOT (AST)
    SGPT (ALT)
    Alkaline Phosphatase
    Gamma glutamyl transferase (GGT)
    Lactate dehydrogenase (LDH)
Other:
    Creatinine
    Blood urea nitrogen (BUN)
    BUN/creatinine ratio
    Bilirubin, total
    Protein, total
    Albumin
    Uric acid

Glucose
HIV-1/2 antibody
Hepatitis C **antibody (± HCV RNA PCR for confirmation of positive antibody test)**
Hepatitis B surface antigen
Hepatitis B surface and core antigen antibodies
Estimated Creatinine Clearance/ GFR (Cockcroft-Gault)

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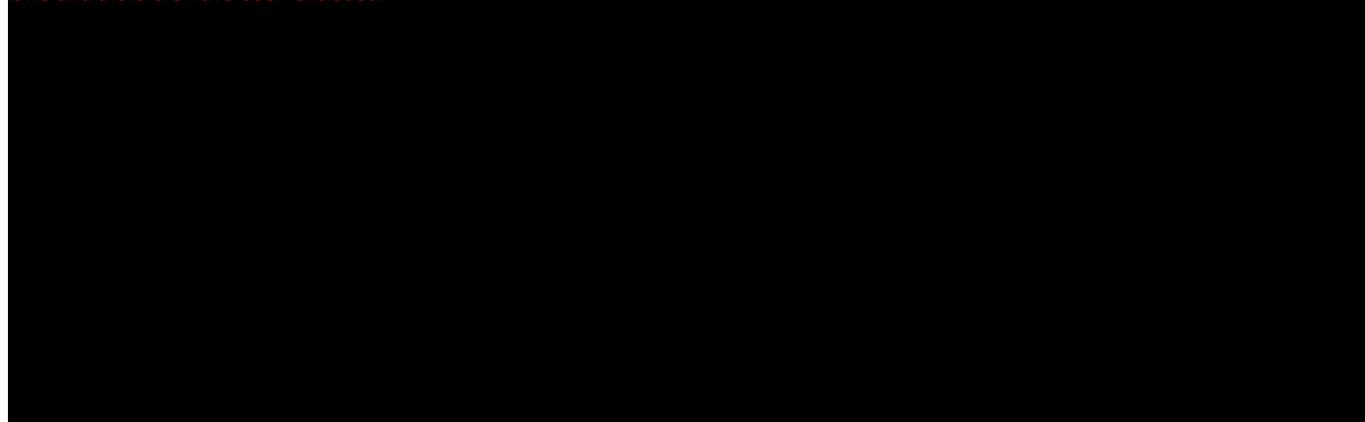   **Type 1 anti-liver kidney microsomal antibodies**

Footnote added:

Appendix 6 Laboratory Tests[1]

[1]   **Institution or country specific guidelines for blood sample volume limits must be followed in collection of the subsequent blood sample.**

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

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

Modified to:

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

Appendix 9 Pharmacogenetic Research, Research Rationale

Formerly:

Systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies but little is known regarding the genetic contribution to risk for developing different forms of vasculitis. Recent gene studies in vasculitis are identifying both common polymorphisms associated with other autoimmune but also completely different associations.

There is growing evidence for a genetic contribution to the risk of developing different forms of vasculitis (Monach, 2010) for example the association of alpha 1-antitrypsin deficiency in WG.

Modified to:

Systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies but little is known regarding the genetic contribution to risk for developing different forms of vasculitis. Recent gene studies in vasculitis are identifying both common polymorphisms associated with other autoimmune but also completely different associations **(Monach and Merkel, 2010)**.

There is growing evidence for a genetic contribution to the risk of developing different forms of vasculitis (Monach **and Merkel,** 2010) for example the association of alpha 1-antitrypsin deficiency in WG.

Appendix 10 Possible Suicidality Related History Questionnaire (PSRHQ)

Added:

CONFIDENTIAL

gsk GlaxoSmithKline | **Protocol Identifier** | **BEL115466** | Final - 16 JAN 13

POSSIBLE SUICIDALITY-RELATED HISTORY QUESTIONNAIRE (PSRHQ) INSTRUCTIONS

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

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

And/or

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

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

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

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

gsk GlaxoSmithKline   CONFIDENTIAL   Final - 16 JAN 13

Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
BEL115466			_____

Date of assessment [ ] [ ] [ ] [ ] [ ] [ ]
                    Day   Month   Year

POSSIBLE SUICIDALITY-RELATED HISTORY QUESTIONNAIRE

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

[Y] ☐ Yes   [N] ☐ No

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

	Event	Date (DDMMMYYYY)
☐	Cerebrovascular Accident	
☐	Headache	
☐	Meningitis	
☐	Organic Confusion	
☐	Seizures	

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

Appendix 11 Possible Suicidality Related Questionnaire (PSRQ)

Added:

CONFIDENTIAL

gsk GlaxoSmithKline | **Protocol Identifier** | **BEL115466** | Final - 15 JAN 13

POSSIBLE SUICIDALITY-RELATED QUESTIONNAIRE (PSRQ) INSTRUCTIONS

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

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

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

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

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

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

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

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

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

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

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Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
BEL115466			

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

POSSIBLE SUICIDALITY-RELATED QUESTIONNAIRE (PSRQ)

☐ **Not Done**

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

If Yes, check all that apply:

☐ Amphetamines ☐ Benzodiazepines ☐ Cannabinoids ☐ Cocaine ☐ Opiates

☐ Other, Specify: _____

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

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

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

If Yes, check all that apply:

☐ Family Problems ☐ Relationships ☐ Employment/ Unemployment ☐ Finances

☐ Other Factors, Specify:_____

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

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

Father   ☐ Ideation   ☐ Behavior

Mother   ☐ Ideation   ☐ Behavior

Sibling   ☐ Ideation   ☐ Behavior

Other   ☐ Ideation   ☐ Behavior

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

If Yes, specify disorder next to all that apply:

Father   _____

Mother   _____

Sibling   _____

Other   _____

Appendix 12 Protocol Addendum – Benefit and Risk Assessment

Added:

Disease Background

The systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies including infective and drug-induced causes and can be either primary or secondary to other diseases such as SLE. A subset of the primary small vessel vasculitides: Wegener's granulomatosis; also known as granulomatosis with polyangiitis (GPA), microscopic polyangiitis and Churg-Strauss syndrome (CSS), are characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) (Jennette and Falk, 1997). ANCA-associated vasculitides (AAV) are multisystem diseases with a broad range of manifestations from cutaneous ulcers, scleritis, pericarditis to lifethreatening manifestations such as lung hemorrhage and renal failure. All 3 forms of AAV share the characteristic of systemic necrotizing vasculitis; WG and CSS are further characterized by granuloma formation.

Historically, ANCA have been classified on the basis of their staining patterns in immunofluoresence assays as either cytoplasmic (C-ANCA) or perinuclear (P-ANCA). It is now recognized that in AAV, C-ANCA is usually directed against proteinase 3 (PR3), and P-ANCA is generally directed against myeloperoxidase (MPO), both of which are enzymes that are abundant in the granules of neutrophils (Jennette and Falk, 1997; Merkel et al, 1997). Anti-PR3 antibodies are generally associated with WG, while anti-MPO autoantibodies are more common in MPA and CSS. Anti-PR3 antibodies are associated with increased morbidity and mortality compared to anti-MPO. The most widely used classification criteria for diagnosing the 3 types of AAV are those published by the American College of Rheumatology (ACR) for WG and CSS (Leavitt et al, 1990 and Masi et al, 1990, respectively), and that published by the Chapel Hill Consensus Conference (CHCC) for MPA (Jennette et al, 1994). Of note, none of these diagnostic criteria incorporate the measurement of ANCA.

The precise epidemiology of these diseases is uncertain as early studies did not utilize the same classification criteria as later ones (Koldingsnes and Nossent, 2008; Watts et al, 2007). In the case of MPA, in particular, epidemiological studies are confounded by its original inclusion as a form of polyarteritis nodosa (PAN). Utilizing the ACR or CHCC criteria, prevalence rates range from 5-16/100000 for WG, 2.5-9.4/100000 for MPA, and 0.4-1.4/100000 for CSS making the latter the least prevalent of the three by some margin (Koldingsnes et al, 2008). AAV are extremely rare in childhood with peak age of onset in those aged 65 to 74 years (Ntatski et al, 2010), with other small vessel vasculitides being the major concern in childhood (Brogan et al, 2010).Current therapy is usually determined by severity of the disease, with more severe forms warranting more aggressive approaches. These usually involve an initial remission induction regimen of high dose corticosteroid administered with either cyclophosphamide (CYC) or rituximab (RTX) followed by a remission maintenance period usually with azathioprine (Stone et al, 2010; Bosch et al, 2007; Jayne et al, 2003). Minor manifestations are usually treated with low dose corticosteroid

administered with either azathioprine or methotrexate (Belmont, 2006). Even with recent treatment advances the morbidity and mortality of patients with AAV remains unacceptably high (Drooger et al, 2009).

The Birmingham Vasculitis Activity Score (BVAS) was developed and validated as a tool to measure disease activity (Luqmani et al, 1994). It has been modified to form the BVAS/WG (Stone et al, 2001) and updated most recently with the validation of version 3 of the instrument, also known as BVAS 2003 (Mukhtyar et al, 2009). In its current form it is a list of 56 items which are considered to be manifestations of vasculitis. A weighted numerical score is attached to each item to reflect the importance of each manifestation. The items are grouped by organ systems, and each organ system has a maximum or 'ceiling' score to reflect the relative importance of the organ system (Mukhtyar et al, 2009). The tool also makes a distinction between new or worsening disease and persistent disease with new or worsening attracting higher scores.

IV Belimumab

Over 2,000 individuals with SLE have been treated with belimumab in clinical studies. In two global Phase 3 studies, belimumab 10 mg/kg met the primary efficacy endpoint (SRI at Week 52). Evidence of other possible benefits in these trials included reductions in risk of severe flare and corticosteroid use, and improvements in patient reported quality of life and fatigue. Serological activity was reduced as measured by reductions in autoantibodies and normalization of hypergammaglobulinemia and complement levels. B cells, including autoreactive B cells, were also reduced, but not severely depleted, consistent with what would be expected from inhibition of BLyS (reference belimumab IB, Section 5.3.1). These results supported the approval of belimumab in the EU, US, Canada and other countries.

In the United States belimumab is approved for the following indication:

> *BENLYSTA® (belimumab) is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.*
>
> *Limitations of Use: The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of BENLYSTA is not recommended in these situations.*

In the EU, the approved indication focuses on patients with high disease activity (where belimumab offered the greatest benefit):

> *Benlysta is indicated as add-on therapy in adult patients with active, autoantibodypositive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g positive anti-dsDNA and low complement) despite standard therapy.*

The EU SPC also includes special warnings and precautions for use similar to the US labeling, including that belimumab has not been studied in and is thus not recommended in

patients with severe active central nervous system lupus or severe active lupus nephritis. In addition, caution should be exercised if belimumab is co-administered with other B cell targeted therapy or cyclophosphamide. Reference Section 4.4 of the SPC for the complete list of specials warnings and precautions.

Treatment with belimumab plus standard therapy was generally well tolerated, with rates of AEs, severe AEs, SAEs, AEs leading to discontinuation, and serious/severe infections generally comparable to the rates observed in the placebo plus standard therapy group. The most commonly-reported adverse reactions, occurring in $\geq 3\%$ of patients receiving 10 mg/kg belimumab IV in clinical trials (and at a $\geq 1\%$ greater rate than placebo) were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, cystitis, leukopenia, and gastroenteritis viral. In clinical trials, hypersensitivity and infusion reactions were observed more frequently with belimumab, with anaphylaxis observed in $\leq 1\%$ of subjects. Data from the post-marketing setting indicate that hypersensitivity reactions may be serious or result in death, that the onset of such reactions may be delayed, and that patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. In addition, it is also known from clinical trials and the post-marketing setting that the vast majority of hypersensitivity reactions occur with the 1st or 2nd infusion. The product labeling, belimumab IB, protocol, and informed consent forms have been updated to include this new information, as applicable.

Other risks that may be associated with belimumab based on its mechanism of action include serious infections and malignancy, although no increases in the rates of serious infections or malignancies have been observed. Psychiatric events including depression and suicide were observed more frequently with belimumab than with placebo, although it is unknown if belimumab treatment is associated with an increased risk for these events. Finally, mortality rates in the controlled clinical trials were low, although numerically higher in the belimumab groups (0.4% and 0.8% in the placebo and belimumab groups, respectively). Causes of death were as expected in an SLE population with active disease receiving a wide range of standard therapies, such as corticosteroids and immunosuppressants, and included infection, cardiovascular disease, and suicide.

Experience from open-label, long-term continuation trials of belimumab in SLE patients suggests prolonged treatment with belimumab remains generally well tolerated, with no apparent increase in the incidence of AEs or 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.

Belimumab in ANCA-Associated Vasculitis

Study Overview and Patient Population

Belimumab at a dose of 10 mg/kg in combination with standard SLE therapy demonstrated a statistically significant and clinically meaningful reduction in SLE disease activity versus placebo plus standard SLE therapy at Week 52 in two Phase 3 clinical studies in subjects with active, autoantibody-positive SLE.

Studies in subjects with WG and MPA have shown the need for more effective treatment for the maintenance of remission, with relapse rates with these 2 diseases ranging from 15% at 18 months (Jayne et al, 2003) to 38% at 3 years (Hiemstra et al, 2010) on azathioprine – the most effective of current therapies (Jayne et al, 2003; Pagnoux et al, 2008; Hiemstra et al, 2010).

The presence of ANCA autoantibodies in AAV implicates B cells in the pathogenesis of AAV. Further supporting a role for B cells is the fact that activated B cells are present in greater numbers in GPA subjects compared with healthy persons (Popa et al, 1999). Additionally, elevated levels of BLyS, a B cell survival factor, are found in subjects with AAV (Krumbholz et al, 2005; Nagai et al, 2011; Schneeweis et al, 2010). Together, these provide a strong pharmacologic rationale for the use of belimumab to treat AAV, since belimumab has been shown in SLE to reduce both B cells and autoantibody levels. Therefore, for the proposed study, subjects are required to have documented evidence of anti-PR3 or anti-MPO autoantibodies prior to randomization, as this population is considered the most likely to benefit from treatment with a B cell modulating agent like belimumab. This is consistent with the Phase 3 SLE results for belimumab where the subjects who benefitted from treatment were those who were antinuclear antibody (ANA/anti-dsDNA) autoantibody positive at baseline.

The fact that rituximab, a biologic therapy that targets B cells by binding to the B cell surface antigen CD20, recently showed success in inducing remission in AAV (Stone et al, 2010) and was granted approval in the US for the treatment of WG and MPA supports the rationale that belimumab, which down regulates B cells by targeting BLyS, may be useful in the treatment of this disease. Finally, limited data from the small (n = 111) subset of subjects in the Phase 3 trials of SLE who had vasculitic symptoms as part of their SLE (as assessed by the SELENA SLEDAI) showed that more subjects in the belimumab plus standard of care treatment arms had resolution of their vasculitic symptoms at Week 52 compared with subjects receiving placebo plus standard of care. Specifically, 19/36 (52.8%) and 28/38 (73.7%) of subjects in the belimumab 1 mg/kg and 10 mg/kg dose groups, respectively, had resolution of vasculitic activity at Week 52 compared with 15/37 (40.5%) of placebo subjects. Taken together, these data support the evaluation of belimumab in AAV.

The safety of the proposed study is supported by data from the Phase 2 and 3 trials in SLE in which subjects who were receiving belimumab in combination with significant background therapies, including steroids and immunosuppressants, had an adverse event profile similar to that of subjects receiving placebo plus standard therapies.

This is a Phase 3, multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen. Subjects enrolled into the study must have a clinical diagnosis of WG or MPA according to the Chapel Hill criteria and must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either CYC or RTX in the 6 months leading up to randomization. Subjects treated with 1 of the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- CYC 2 mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The doses of CYC are given as targets but may be adjusted for renal insufficiency or white cell counts as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach < 10 mg/day.

A target of 300 to 400 subjects who are within 26 weeks of starting induction therapy, achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving less than 10 mg/day prednisone (or equivalent) on 2 consecutive measurements 21 to 35 days apart will be enrolled into the study. Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour. Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter. Randomization will be performed on Day 0. Day 0 (first administration of belimumab/placebo) must occur no more than 2 weeks after confirmation of remission.

All subjects (in both the belimumab and placebo groups) will be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. Azathioprine must be initiated at any time following confirmation of remission up to and including Day 0. Patients with known intolerance to azathioprine will be excluded from the trial. Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above, a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis.

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV CYC vs. oral CYC vs. RTX). It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Refer to Section 4 of Protocol HGS1006-C1100 for a complete list of inclusion and exclusion criteria.

The primary efficacy endpoint is time from Day 0 to the first relapse, defined as at least 1 major BVAS item or a minimum total BVAS score of 6 or receipt of prohibited medications

according to the protocol. Subjects will receive study agent (belimumab/placebo) plus AZA until the results from the primary efficacy analysis are available or until they experience a flare (relapse) as defined in the primary efficacy endpoint. The database will be locked and the primary analysis will be performed after at least 66 subjects have experienced a relapse and at least 12 months have elapsed after the last subject is randomized. Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an attempt will be made to ascertain survival status at 12 months after the first dose of study agent.

If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in a 6-month open-label extension period, in which all subjects will receive 10 mg/kg belimumab IV. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety. All subjects will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent. These visits apply to subjects who have completed as well as those who have withdrawn early from the open-label extension.

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

Dose and Schedule

Investigational Study Agent (Belimumab or Placebo)

The dose and schedule of belimumab proposed for use in the ANCA-associated vasculitis study is the same dosage (10 mg/kg every 2 weeks for 3 doses and every 4 weeks thereafter) and route of administration (IV) as that approved for marketing. The belimumab BDS and FDP that will be used for this study is the same as that approved for marketing.

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

the marketed dose in general SLE, and also support its continued evaluation in combination with standard maintenance therapies in patients with WG or MPA.

The use of placebo in this trial is considered appropriate and does not put placebo patients at undue risk because all subjects in both the placebo group and the belimumab group will receive standard of care maintenance therapies for vasculitis (ie, azathioprine or methotrexate) and, if needed, subjects will receive appropriate rescue therapy in accordance with standard clinical practice as described above.

Induction and Maintenance Regimens for ANCA-Associated Vasculitis

Subjects participating in this trial will have had a moderate to severe episode of WG or MPA that was treated with high-dose corticosteroids (HDCS) and either RTX or CYC (IV or oral) to induce the remission of the disease. Subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- CYC 2mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The doses of cyclophosphamide are given as targets but may be adjusted for renal insufficiency or white cell counts as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach < 10 mg/day.

Rituximab was approved in April 2011 by the FDA for the treatment of WG and MPA. It has been used in induction of remission in AAV for a number of years, (Gorman et al, 2003, Smith et al, 2006) and 2 recent trials published in 2010 (Stone et al, 2010), demonstrated non-inferiority to induction with cyclophosphamide, the latter of these trials being used as the basis for the recent US approval. The RTX regimen specified in this vasculitis study is the same as that approved by the FDA for this indication.

Cyclophosphamide (2 mg/kg/day orally or IV 15 mg every 2 weeks for 3 doses and every 3 weeks thereafter) plus prednisone has been the standard induction regimen for WG and MPA since the early 1970s when initial work by Fauci and Wolff at the National Institutes of Health showed that this regimen induced disease remission in 12/14 patients and subsequent work showed that survival rates increased 80% using this regimen in what was previously an uniformly fatal disease (Fauci and Wolff, 1973; Fauci et al, 1983; Hoffman et al, 1992; Langford, 2011). Long term continued cyclophosphamide use, however, has been associated with significant toxicities (including infection, cystitis, cytopenias, and long term complications such as myelodysplasia and bladder cancer) and mortality (Langford, 2011).

A more recent study conducted by the European Vasculitis Group (Jayne et al, 2003) showed that after initial disease remission with cyclophosphamide and steroids, subjects could be switched to azathioprine (2 mg/kg/day) without having an increased risk of relapse compared to subjects whose remission was maintained using continued cyclophosphamide treatment. An induction regimen of CYC + prednisone followed by maintenance treatment with azathioprine is now considered the standard of care, given that administration of cyclophosphamide for longer durations does not offer an advantage from an efficacy standpoint and is associated with a greater potential for toxicity (Langford, 2011). The cyclophosphamide regimens described above are the same as those allowed in the inclusion criteria for this vasculitis study.

Once disease remission (defined as having, on 2 consecutive measurements 3 to 5 weeks apart: a BVAS v3 score of 0 and be receiving < 10 mg/day of oral prednisone [or equivalent], achieved no more than 26 weeks after the first dose of induction therapy) has been achieved, subject randomization into this protocol occurs. In this maintenance of remission trial, subjects will be randomized to receive a maintenance regimen of AZA (2 mg/kg/day) + placebo or AZA (2 mg/kg/day) + belimumab (10 mg/kg). Randomization in this protocol must occur within 2 weeks of achieving a confirmed remission and the randomization will be stratified by induction regimen.

The primary safety population for the SLE indication, including 473 subjects who were taking azathioprine as a concomitant medication at baseline, provides a substantial amount of safety data to support the conduct of the proposed trial. In this study, subjects who have a known intolerance to azathioprine will be excluded. Subjects naive to azathioprine and who experience azathioprine-related toxicity (Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT 2 times ULN, or a several gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting), following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience toxicities, a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis. The protocol instructs physicians to follow the appropriate local prescribing information for azathioprine or methotrexate (as applicable) prior to and during treatment.

Input on selection of these standard of care regimens was obtained from international experts in vasculitis, including members of the European Vasculitis Society (EUVAS) and the Vasculitis Clinical Research Consortium (VCRC), and consensus was reached that these regimens are appropriate for this international trial.

Complete details regarding the use of concurrent medications can be found in Section 5.5 of Protocol HGS1006-C1100.

Safety Considerations

An independent Data Monitoring Committee (DMC) will review safety data on an ongoing basis until the data are locked and analyzed (after which monitoring may be assumed by an internal HGS committee). The DMC will include at least 3 physicians and a statistician, none of whom are affiliated with the Sponsor. Belimumab has not yet been studied following use of IV cyclophosphamide (CYC) or rituximab (RTX); there is limited experience with the combination of belimumab and oral CYC. As an added safety precaution, initial randomization will be limited to 40 subjects per induction regimen (40 post-RTX induction and 40 post-CYC induction). The first DMC reviews will occur after the first 20 subjects per induction regimen (RTX or IV/oral CYC) have been randomized and have had a Week 8 visit. Once the first 20 subjects randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the DMC, who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with CYC. The DMC will review the data approximately every 6 months thereafter across both induction regimens. At all times the patients, study sites and sponsor will remain blinded to treatment allocation. Investigators and IRBs/IECs will be notified of the outcome of each DMC meeting.

The DMC will be notified of:

- • all unexpected causally-related SAEs that are life-threatening or result in death;
- • other unexpected causally-related SAEs;
- • all reports of serious infections and opportunistic infections, irrespective of relationship to study agent; and
- • subjects experiencing IgG < 250 mg/dL;

within protocol-specified timeframes. Based on these data, an ad hoc DMC meeting may be called at any time (see Section 8.3 of Protocol HGS1006-C1100 for additional detail regarding the DMC).

Based on the large body of safety data from SLE patients treated with belimumab and/or the mechanism of action of belimumab as a B cell immunosuppressant, anticipated potential risks of belimumab treatment in vasculitis patents include serious infusion and hypersensitivity reactions, infections, depression-related events, and malignancy. These risks are briefly reviewed here and are detailed more fully in the belimumab Investigator's Brochure. Both investigators and subjects will be appropriately informed regarding these risks. It is noted that because of the older patient population affected by this disease, the average age of subjects anticipated to participate in this study will be older than the average age of the SLE population studied to date (mean age of ~53 years at the time of diagnosis in vasculitis (Stone et al, 2010) compared with an average age of ~38 years in controlled Phase 3 studies of belimumab in SLE). As such, patients with vasculitis may be at a greater risk for infection than the SLE patients; however, the increased monitoring for infections by both the DMC (described above) and recommended to investigators (see below) will help to ensure subject safety through timely detection, treatment and reporting of infections.

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

In order to ensure subject safety with respect to infusion and hypersensitivity reactions, the protocol excludes patients with known history of allergic reactions to human or murine proteins or monoclonal antibodies. There is currently insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions to belimumab. The protocol recommends that based on clinical judgment, premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion. Antihistamine H2-receptor antagonists (eg, ranitidine) are also permitted. Belimumab/placebo will be administered by investigators/site personnel prepared to manage infusion reactions and anaphylaxis. The infusion rate may be slowed or interrupted if the subject develops an infusion reaction. Investigators/site personnel should be aware of the risk of hypersensitivity reactions, which may present as infusion reaction, and monitor subjects closely. In the event of a serious reaction, belimumab/placebo administration must be discontinued immediately and the appropriate medical therapy administered. Per protocol, subjects are to remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase and the open-label extension. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing for any untoward reactions. Beyond the first 2 infusions, subjects should be monitored during and for an appropriate period of time after infusion according to study sites' guidelines or standard operating procedure for IV infusions. Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

The protocol recommends that subjects with persistent or worsening disease should receive appropriate rescue therapy in accordance with standard clinical practice, but if exceeding what is allowed per protocol, treatment with study agent (ie, belimumab or placebo) will be discontinued and the subject will be considered as having relapsed for the primary analysis. The list of prohibited medications that results in the subjects being considered as relapsed for the primary endpoint (Protocol Section 5.5.2.1), was developed because the need for the use of these agents (eg, RTX or CYC) is indicative of treatment failure (ie, disease relapse).

Moreover, concomitant use of such medications (eg, high-dose steroids) can be associated both with potent disease-modifying activity and/or significant toxicity that may introduce

bias and confound interpretation of results. As such, no subject will be denied appropriate medical care for their condition due to their participation in this clinical study.

In addition, the Sponsor notes that although this is a placebo controlled trial, the sponsor does not consider that placebo patients are at undue risk because all subjects in both the placebo group and the belimumab group will receive standard of care maintenance therapies for vasculitis (ie, azathioprine or methotrexate) and, if needed, subjects will receive appropriate rescue therapy in accordance with standard clinical practice as described above.

Risk:Benefit Conclusions

In summary, the proposed Phase 3 study is a superiority study evaluating the safety and efficacy of belimumab for the maintenance of disease remission in patients with a clinical diagnosis of Wegener's granulomatosis or microscopic polyangiitis. The risk:benefit profile of 10 mg/kg IV belimumab in patients with active, autoantibody-positive SLE was demonstrated to be positive in the two Phase 3 SLE studies, thereby supporting its approval in Canada, the US, and the EU. Belimumab has already been shown to be effective in treating patients with active, autoantibody-positive SLE, a B cell mediated autoimmune disease. Like SLE, WG and MPA are also B cell mediated autoimmune diseases in which autoantibodies (in this case, against neutrophil components), are considered to be pathogenic (Popa et al, 1999). In each of these diseases, the general purpose of the therapy is similar – reducing disease activity by down regulating B cells (including autoreactive B cells) and reducing the level autoantibodies produced by those autoreactive B cell clones. Down regulating B cell numbers may also reduce inflammatory processes because of the role of B cells in antigen presentation. A limited amount of data from the IV Phase 3 studies suggests that belimumab may reduce vasculitic symptoms.

There are potential risks associated with belimumab treatment including serious infusion and hypersensitivity reactions, infections, depression-related events, and malignancy; however, in view of the serious and potentially life threatening nature of disease flares in WG and MPA, it is believed that the overall risk:benefit analysis for belimumab in the maintenance of remission in WG and MPA is favorable, especially in view of the nature of the trial as a superiority trial over a current standard of care regimen.

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Protocol HGS1006-C1100-01 Addendum 01 (Ireland) Summary of Modifications   Belimumab

Local Addendum 01 for Ireland, 31 January 2013
Protocol Number: HGS1006-C1100-01

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The protocol has been modified, at the request of the Irish Medicines Board, to ensure consistency with the current Summary of Product Characteristics for azathioprine with respect to recommendations for the frequency of monitoring complete blood count.

Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment: 01
Date: 22 June 2012

Modified to:

Protocol Amendment: 01
Date: 22 June 2012
Local Addendum 01 for Ireland, Date: 31 January 2013

List of Abbreviations

Added:

SmPC   Summary of Product Characteristics

Section 5.5.3.1 Azathioprine and Methotrexate

Formerly:

It is recommended that the appropriate local prescribing information (eg, contraindications, hematological and biochemical monitoring, pregnancy, contraception, etc.) for azathioprine or methotrexate (MTX) (as applicable), should be followed prior to and during treatment.

In the extension phase of the trial, the dose of AZA/MTX can be decreased or discontinued based on the discretion of the investigator.

Modified to:

It is recommended that the appropriate local prescribing information (eg, contraindications, hematological and biochemical monitoring, pregnancy, contraception, etc.) for azathioprine or methotrexate (MTX) (as applicable), should be followed prior to and during treatment.

As per the Summary of Product Characteristics (SmPC) for azathioprine, it is suggested that during the first 8 weeks of therapy, complete blood counts, including platelets, should be performed weekly or more frequently if high dosage is used or if severe renal and/or hepatic disorder is present. The blood count frequency may be reduced later in therapy, but it is suggested that complete blood counts are repeated monthly, or at least at intervals of not longer than 3 months.

In the extension phase of the trial, the dose of AZA/MTX can be decreased or discontinued based on the discretion of the investigator.

**Table 6-1 Double-blind Treatment Year One
Hematology & Modified Chem-20 (non-fasting)
Day 0Visit**

Formerly:

"X"

Modified to:

"X[15]"

**Table 6-1 Double-blind Treatment Year One
Hematology & Modified Chem-20 (non-fasting)
Week 2 Visit**

Formerly:

"X"

Modified to:

"X[16]"

Table 6-1 Double-blind Treatment Year One
Hematology & Modified Chem-20 (non-fasting)
Week 4 Visit

Formerly:

"X"

Modified to:

"X[17]"

Table 6-1 Double-blind Treatment Year One
Footnotes

Added:

15. In addition, at Week 1, a complete blood count including hemoglobin, hematocrit, RBC, platelet count, total white blood cell count, and differential white blood cell count should be performed.

16. In addition, at Week 3, a complete blood count including hemoglobin, hematocrit, RBC, platelet count, total white blood cell count, and differential white blood cell count should be performed.

17. In addition, at Weeks 5, 6 and 7, a complete blood count including hemoglobin, hematocrit, RBC, platelet count, total white blood cell count, and differential white blood cell count should be performed.

Table 6-3 Open-Label Extension Phase
Row, Hematology & Modified Chem-20 (non-fasting)
Week 12Visit

Formerly:

"X"

Modified to:

"X[11]"

2013N160488_00

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Protocol HGS1006-C1100-01 Addendum 01 (Ireland) Summary of Modifications   Belimumab

Table 6-3 Open-Label Extension Phase
Footnotes

Added:

11 A complete blood count including hemoglobin, hematocrit, RBC, platelet count, total white blood cell count, and differential white blood cell count should be performed.

<div align="center">

Local Addendum 01 for Sweden, 29 January 2013
Protocol Number: HGS1006-C1100-01

</div>

Protocol Title: A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis

Summary of Modifications and Rationale:

1. The protocol has been modified to include a Benefit and Risk Assessment (Appendix 10) at the request of the Swedish Regulatory Authority. The List of Appendices has been updated accordingly.

Associated Protocol Modifications:

Protocol Cover Page

Formerly:

Protocol Amendment: 01
Date: 22 June 2012

Modified to:

Protocol Amendment: 01
Date: 22 June 2012
Local Addendum 01 for Sweden, Date: 29 Jan 2013

Appendix 10 Protocol Addendum – Benefit and Risk Assessment

Added:

Disease Background

The systemic vasculitides encompass a range of diseases affecting different sizes of blood vessels with a variety of etiologies including infective and drug-induced causes and can be either primary or secondary to other diseases such as SLE. A subset of the primary small vessel vasculitides: Wegener's granulomatosis; also known as granulomatosis with polyangiitis (GPA), microscopic polyangiitis and Churg-Strauss syndrome (CSS), are characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) (Jennette and Falk, 1997). ANCA-associated vasculitides (AAV) are multisystem diseases with a broad range of manifestations from cutaneous ulcers, scleritis, pericarditis to lifethreatening manifestations such as lung hemorrhage and renal failure. All 3 forms of AAV share the characteristic of systemic necrotizing vasculitis; WG and CSS are further characterized by granuloma formation.

Historically, ANCA have been classified on the basis of their staining patterns in immunofluoresence assays as either cytoplasmic (C-ANCA) or perinuclear (P-ANCA). It is now recognized that in AAV, C-ANCA is usually directed against proteinase 3 (PR3), and P-ANCA is generally directed against myeloperoxidase (MPO), both of which are enzymes that are abundant in the granules of neutrophils (Jennette and Falk, 1997; Merkel et al, 1997). Anti-PR3 antibodies are generally associated with WG, while anti-MPO autoantibodies are more common in MPA and CSS. Anti-PR3 antibodies are associated with increased morbidity and mortality compared to anti-MPO. The most widely used classification criteria for diagnosing the 3 types of AAV are those published by the American College of Rheumatology (ACR) for WG and CSS (Leavitt et al, 1990 and Masi et al, 1990, respectively), and that published by the Chapel Hill Consensus Conference (CHCC) for MPA (Jennette et al, 1994). Of note, none of these diagnostic criteria incorporate the measurement of ANCA.

The precise epidemiology of these diseases is uncertain as early studies did not utilize the same classification criteria as later ones (Koldingsnes and Nossent, 2008; Watts et al, 2007). In the case of MPA, in particular, epidemiological studies are confounded by its original inclusion as a form of polyarteritis nodosa (PAN). Utilizing the ACR or CHCC criteria, prevalence rates range from 5-16/100000 for WG, 2.5-9.4/100000 for MPA, and 0.4-1.4/100000 for CSS making the latter the least prevalent of the three by some margin (Koldingsnes et al, 2008). AAV are extremely rare in childhood with peak age of onset in those aged 65 to 74 years (Ntatski et al, 2010), with other small vessel vasculitides being the major concern in childhood (Brogan et al, 2010).Current therapy is usually determined by severity of the disease, with more severe forms warranting more aggressive approaches. These usually involve an initial remission induction regimen of high dose corticosteroid administered with either cyclophosphamide (CYC) or rituximab (RTX) followed by a remission maintenance period usually with azathioprine (Stone et al, 2010; Bosch et al, 2007; Jayne et al, 2003). Minor manifestations are usually treated with low dose corticosteroid administered with either azathioprine or methotrexate (Belmont, 2006). Even with recent treatment advances the morbidity and mortality of patients with AAV remains unacceptably high (Drooger et al, 2009).

The Birmingham Vasculitis Activity Score (BVAS) was developed and validated as a tool to measure disease activity (Luqmani et al, 1994). It has been modified to form the BVAS/WG (Stone et al, 2001) and updated most recently with the validation of version 3 of the instrument, also known as BVAS 2003 (Mukhtyar et al, 2009). In its current form it is a list of 56 items which are considered to be manifestations of vasculitis. A weighted numerical score is attached to each item to reflect the importance of each manifestation. The items are grouped by organ systems, and each organ system has a maximum or 'ceiling' score to reflect the relative importance of the organ system (Mukhtyar et al, 2009). The tool also makes a distinction between new or worsening disease and persistent disease with new or worsening attracting higher scores.

IV Belimumab

Over 2,000 individuals with SLE have been treated with belimumab in clinical studies. In two global Phase 3 studies, belimumab 10 mg/kg met the primary efficacy endpoint (SRI at

Week 52). Evidence of other possible benefits in these trials included reductions in risk of severe flare and corticosteroid use, and improvements in patient reported quality of life and fatigue. Serological activity was reduced as measured by reductions in autoantibodies and normalization of hypergammaglobulinemia and complement levels. B cells, including autoreactive B cells, were also reduced, but not severely depleted, consistent with what would be expected from inhibition of BLyS (reference belimumab IB, Section 5.3.1). These results supported the approval of belimumab in the EU, US, Canada and other countries.

In the United States belimumab is approved for the following indication:

> *BENLYSTA® (belimumab) is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.*

> *Limitations of Use: The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of BENLYSTA is not recommended in these situations.*

In the EU, the approved indication focuses on patients with high disease activity (where belimumab offered the greatest benefit):

> *Benlysta is indicated as add-on therapy in adult patients with active, autoantibodypositive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g positive anti-dsDNA and low complement) despite standard therapy.*

The EU SPC also includes special warnings and precautions for use similar to the US labeling, including that belimumab has not been studied in and is thus not recommended in patients with severe active central nervous system lupus or severe active lupus nephritis. In addition, caution should be exercised if belimumab is co-administered with other B cell targeted therapy or cyclophosphamide. Reference Section 4.4 of the SPC for the complete list of specials warnings and precautions.

Treatment with belimumab plus standard therapy was generally well tolerated, with rates of AEs, severe AEs, SAEs, AEs leading to discontinuation, and serious/severe infections generally comparable to the rates observed in the placebo plus standard therapy group. The most commonly-reported adverse reactions, occurring in $\geq 3\%$ of patients receiving 10 mg/kg belimumab IV in clinical trials (and at a $\geq 1\%$ greater rate than placebo) were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, cystitis, leukopenia, and gastroenteritis viral. In clinical trials, hypersensitivity and infusion reactions were observed more frequently with belimumab, with anaphylaxis observed in $\leq 1\%$ of subjects. Data from the post-marketing setting indicate that hypersensitivity reactions may be serious or result in death, that the onset of such reactions may be delayed, and that patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. In addition, it is also known from clinical trials and the post-marketing setting that the vast majority of hypersensitivity reactions occur with the

1st or 2nd infusion. The product labeling, belimumab IB, protocol, and informed consent forms have been updated to include this new information, as applicable.

Other risks that may be associated with belimumab based on its mechanism of action include serious infections and malignancy, although no increases in the rates of serious infections or malignancies have been observed. Psychiatric events including depression and suicide were observed more frequently with belimumab than with placebo, although it is unknown if belimumab treatment is associated with an increased risk for these events. Finally, mortality rates in the controlled clinical trials were low, although numerically higher in the belimumab groups (0.4% and 0.8% in the placebo and belimumab groups, respectively). Causes of death were as expected in an SLE population with active disease receiving a wide range of standard therapies, such as corticosteroids and immunosuppressants, and included infection, cardiovascular disease, and suicide.

Experience from open-label, long-term continuation trials of belimumab in SLE patients suggests prolonged treatment with belimumab remains generally well tolerated, with no apparent increase in the incidence of AEs or 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.

Belimumab in ANCA-Associated Vasculitis

Study Overview and Patient Population

Belimumab at a dose of 10 mg/kg in combination with standard SLE therapy demonstrated a statistically significant and clinically meaningful reduction in SLE disease activity versus placebo plus standard SLE therapy at Week 52 in two Phase 3 clinical studies in subjects with active, autoantibody-positive SLE.

Studies in subjects with WG and MPA have shown the need for more effective treatment for the maintenance of remission, with relapse rates with these 2 diseases ranging from 15% at 18 months (Jayne et al, 2003) to 38% at 3 years (Hiemstra et al, 2010) on azathioprine – the most effective of current therapies (Jayne et al, 2003; Pagnoux et al, 2008; Hiemstra et al, 2010).

The presence of ANCA autoantibodies in AAV implicates B cells in the pathogenesis of AAV. Further supporting a role for B cells is the fact that activated B cells are present in greater numbers in GPA subjects compared with healthy persons (Popa et al, 1999). Additionally, elevated levels of BLyS, a B cell survival factor, are found in subjects with AAV (Krumbholz et al, 2005; Nagai et al, 2011; Schneeweis et al, 2010). Together, these provide a strong pharmacologic rationale for the use of belimumab to treat AAV, since belimumab has been shown in SLE to reduce both B cells and autoantibody levels. Therefore, for the proposed study, subjects are required to have documented evidence of anti-PR3 or anti-MPO autoantibodies prior to randomization, as this population is considered the mostly likely to benefit from treatment with a B cell modulating agent like belimumab. This is consistent with the Phase 3 SLE results for belimumab where the subjects who benefitted from treatment were those who were antinuclear antibody (ANA/anti-dsDNA) autoantibody positive at baseline.

The fact that rituximab, a biologic therapy that targets B cells by binding to the B cell surface antigen CD20, recently showed success in inducing remission in AAV (Stone et al, 2010) and was granted approval in the US for the treatment of WG and MPA supports the rationale that belimumab, which down regulates B cells by targeting BLyS, may be useful in the treatment of this disease. Finally, limited data from the small (n = 111) subset of subjects in the Phase 3 trials of SLE who had vasculitic symptoms as part of their SLE (as assessed by the SELENA SLEDAI) showed that more subjects in the belimumab plus standard of care treatment arms had resolution of their vasculitic symptoms at Week 52 compared with subjects receiving placebo plus standard of care. Specifically, 19/36 (52.8%) and 28/38 (73.7%) of subjects in the belimumab 1 mg/kg and 10 mg/kg dose groups, respectively, had resolution of vasculitic activity at Week 52 compared with 15/37 (40.5%) of placebo subjects. Taken together, these data support the evaluation of belimumab in AAV.

The safety of the proposed study is supported by data from the Phase 2 and 3 trials in SLE in which subjects who were receiving belimumab in combination with significant background therapies, including steroids and immunosuppressants, had an adverse event profile similar to that of subjects receiving placebo plus standard therapies.

This is a Phase 3, multi-center, multinational, randomized, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen. Subjects enrolled into the study must have a clinical diagnosis of WG or MPA according to the Chapel Hill criteria and must have had an initial or relapsing episode of moderate to severely active WG or MPA that was treated with corticosteroids and either CYC or RTX in the 6 months leading up to randomization. Subjects treated with 1 of the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- CYC 2 mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The doses of CYC are given as targets but may be adjusted for renal insufficiency or white cell counts as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach < 10 mg/day.

A target of 300 to 400 subjects who are within 26 weeks of starting induction therapy, achieve a BVAS v.3 score of 0 (ie, are in remission), and are receiving less than 10 mg/day prednisone (or equivalent) on 2 consecutive measurements 21 to 35 days apart will be enrolled into the study. Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to receive study agent (belimumab [10 mg/kg] or placebo) administered intravenously (IV) over 1 hour.

Study agent (belimumab/placebo) will be administered at Day 0, 14, and every 28 days thereafter. Randomization will be performed on Day 0. Day 0 (first administration of belimumab/placebo) must occur no more than 2 weeks after confirmation of remission.

All subjects (in both the belimumab and placebo groups) will be treated with oral azathioprine (AZA) at a dose of 2 mg/kg/day. Azathioprine must be initiated at any time following confirmation of remission up to and including Day 0. Patients with known intolerance to azathioprine will be excluded from the trial. Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT > 2 times ULN, or a severe gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience the toxicities described above, a switch to methotrexate at a target dose of 25 mg/week (and no less than 10 mg/week) as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis.

The randomization will be stratified according to ANCA type (anti-PR3 vs. anti-MPO), disease stage at induction (initial diagnosis vs. relapsing disease), and induction regimen (IV CYC vs. oral CYC vs. RTX). It is anticipated that no more than 25% of the patients would be newly diagnosed and anti-MPO positive, and as such enrollment of these patients may be capped if they exceed this proportion. Refer to Section 4 of Protocol HGS1006-C1100 for a complete list of inclusion and exclusion criteria.

The primary efficacy endpoint is time from Day 0 to the first relapse, defined as at least 1 major BVAS item or a minimum total BVAS score of 6 or receipt of prohibited medications according to the protocol. Subjects will receive study agent (belimumab/placebo) plus AZA until the results from the primary efficacy analysis are available or until they experience a flare (relapse) as defined in the primary efficacy endpoint. The database will be locked and the primary analysis will be performed after at least 66 subjects have experienced a relapse and at least 12 months have elapsed after the last subject is randomized. Subjects who discontinue study agent prior to relapse/flare are to be followed per the double blind visit schedule until relapse/flare or the end of the double-blind treatment phase (whichever is earlier). In subjects who withdraw consent from the study prior to 1 year an attempt will be made to ascertain survival status at 12 months after the first dose of study agent.

If top line data from the double blind portion of this trial show that belimumab is superior to placebo on the primary efficacy endpoint, and the safety profile of belimumab is acceptable, subjects who receive treatment with study agent until the completion of the double-blind period of the study and have not relapsed (as defined by the primary endpoint) will be given the option to receive treatment with belimumab in a 6-month open-label extension period, in which all subjects will receive 10 mg/kg belimumab IV. Subjects participating in the open-label extension will continue to be monitored for efficacy and safety. All subjects will return for an Exit visit approximately 4 weeks after their last dose of study agent as well as a follow-up visit approximately 8 weeks after the last dose of study agent. These visits apply to

subjects who have completed as well as those who have withdrawn early from the open-label extension.

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

Dose and Schedule

Investigational Study Agent (Belimumab or Placebo)

The dose and schedule of belimumab proposed for use in the ANCA-associated vasculitis study is the same dosage (10 mg/kg every 2 weeks for 3 doses and every 4 weeks thereafter) and route of administration (IV) as that approved for marketing. The belimumab BDS and FDP that will be used for this study is the same as that approved for marketing.

In the Phase 3 IV SLE studies, several clinical measures of improvement including the primary efficacy endpoint at Week 52 (SRI), SELENA SLEDAI reductions, severe flare risk reduction, and complement normalization generally favored the 10 mg/kg dose. Trends toward clinically significant steroid reduction were present for both doses. Additionally, there appeared to be a greater dose response in subjects with high disease and serological activity. There was no apparent dose-response in the safety profile of belimumab with both doses being generally well-tolerated. These data supported the selection of 10 mg/kg belimumab as the marketed dose in general SLE, and also support its continued evaluation in combination with standard maintenance therapies in patients with WG or MPA.

The use of placebo in this trial is considered appropriate and does not put placebo patients at undue risk because all subjects in both the placebo group and the belimumab group will receive standard of care maintenance therapies for vasculitis (ie, azathioprine or methotrexate) and, if needed, subjects will receive appropriate rescue therapy in accordance with standard clinical practice as described above.

Induction and Maintenance Regimens for ANCA-Associated Vasculitis

Subjects participating in this trial will have had a moderate to severe episode of WG or MPA that was treated with high-dose corticosteroids (HDCS) and either RTX or CYC (IV or oral) to induce the remission of the disease. Subjects treated under the following induction regimens will be eligible for participation in the study:

- A single course of RTX administered at a dose of 375 mg /m2/week for 4 weeks plus high dose corticosteroids (HDCS) OR
- CYC 2mg/kg/day orally plus HDCS OR
- CYC 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The doses of cyclophosphamide are given as targets but may be adjusted for renal insufficiency or white cell counts as dictated by local practice.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach < 10 mg/day.

Rituximab was approved in April 2011 by the FDA for the treatment of WG and MPA. It has been used in induction of remission in AAV for a number of years, (Gorman et al, 2003, Smith et al, 2006) and 2 recent trials published in 2010 (Stone et al, 2010), demonstrated non-inferiority to induction with cyclophosphamide, the latter of these trials being used as the basis for the recent US approval. The RTX regimen specified in this vasculitis study is the same as that approved by the FDA for this indication.

Cyclophosphamide (2 mg/kg/day orally or IV 15 mg every 2 weeks for 3 doses and every 3 weeks thereafter) plus prednisone has been the standard induction regimen for WG and MPA since the early 1970s when initial work by Fauci and Wolff at the National Institutes of Health showed that this regimen induced disease remission in 12/14 patients and subsequent work showed that survival rates increased 80% using this regimen in what was previously an uniformly fatal disease (Fauci and Wolff, 1973; Fauci et al, 1983; Hoffman et al, 1992; Langford, 2011). Long term continued cyclophosphamide use, however, has been associated with significant toxicities (including infection, cystitis, cytopenias, and long term complications such as myelodysplasia and bladder cancer) and mortality (Langford, 2011).

A more recent study conducted by the European Vasculitis Group (Jayne et al, 2003) showed that after initial disease remission with cyclophosphamide and steroids, subjects could be switched to azathioprine (2 mg/kg/day) without having an increased risk of relapse compared to subjects whose remission was maintained using continued cyclophosphamide treatment. An induction regimen of CYC + prednisone followed by maintenance treatment with azathioprine is now considered the standard of care, given that administration of cyclophosphamide for longer durations does not offer an advantage from an efficacy standpoint and is associated with a greater potential for toxicity (Langford, 2011). The cyclophosphamide regimens described above are the same as those allowed in the inclusion criteria for this vasculitis study.

Once disease remission (defined as having, on 2 consecutive measurements 3 to 5 weeks apart: a BVAS v3 score of 0 and be receiving < 10 mg/day of oral prednisone [or equivalent], achieved no more than 26 weeks after the first dose of induction therapy) has been achieved, subject randomization into this protocol occurs. In this maintenance of remission trial, subjects will be randomized to receive a maintenance regimen of AZA (2 mg/kg/day) + placebo or AZA (2 mg/kg/day) + belimumab (10 mg/kg). Randomization in this protocol must occur within 2 weeks of achieving a confirmed remission and the randomization will be stratified by induction regimen.

The primary safety population for the SLE indication, including 473 subjects who were taking azathioprine as a concomitant medication at baseline, provides a substantial amount of safety data to support the conduct of the proposed trial. In this study, subjects who have a known

intolerance to azathioprine will be excluded. Subjects naive to azathioprine and who experience azathioprine-related toxicity (Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT 2 times ULN, or a several gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting), following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subject continues to experience toxicities, a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted. As azathioprine is among the better tolerated immunomodulatory agents, it is not anticipated that many subjects will need to substitute methotrexate for azathioprine (Walters et al, 2010). Subjects for whom methotrexate is substituted for azathioprine will be included in the primary analysis. The protocol instructs physicians to follow the appropriate local prescribing information for azathioprine or methotrexate (as applicable) prior to and during treatment.

Input on selection of these standard of care regimens was obtained from international experts in vasculitis, including members of the EUVAS and VCRC consortiums, including Dr PPD and Dr PPD and consensus was reached that these regimens are appropriate for this international trial. Please also refer to Sub-Appendix 1 which includes a signed letter from Dr PPD confirming that the induction regimen and maintenance regimen proposed for Study HGS1006-C1100 are currently used as standard of care in clinical practice for the treatment of ANCA-associated vasculitis in Europe.

Complete details regarding the use of concurrent medications can be found in Section 5.5 of Protocol HGS1006-C1100.

Safety Considerations

An independent Data Monitoring Committee (DMC) will review safety data on an ongoing basis until the data are locked and analyzed (after which monitoring may be assumed by an internal HGS committee). The DMC will include at least 3 physicians and a statistician, none of whom are affiliated with the Sponsor. Belimumab has not yet been studied following use of IV cyclophosphamide (CYC) or rituximab (RTX); there is limited experience with the combination of belimumab and oral CYC. As an added safety precaution, initial randomization will be limited to 40 subjects per induction regimen (40 post-RTX induction and 40 post-CYC induction). The first DMC reviews will occur after the first 20 subjects per induction regimen (RTX or IV/oral CYC) have been randomized and have had a Week 8 visit. Once the first 20 subjects randomized following induction with RTX have had a Week 8 visit, safety data will be reviewed by the DMC, who will make a recommendation regarding whether to continue randomization. The same procedure would be applied for the first 20 subjects randomized following induction with CYC. The DMC will review the data approximately every 6 months thereafter across both induction regimens. At all times the patients, study sites and sponsor will remain blinded to treatment allocation. Investigators and IRBs/IECs will be notified of the outcome of each DMC meeting.

The DMC will be notified of:

- • all unexpected causally-related SAEs that are life-threatening or result in death;
- • other unexpected causally-related SAEs;

- • all reports of serious infections and opportunistic infections, irrespective of relationship to study agent; and
- • subjects experiencing IgG < 250 mg/dL;

within protocol-specified timeframes. Based on these data, an ad hoc DMC meeting may be called at any time (see Section 8.3 of Protocol HGS1006-C1100 for additional detail regarding the DMC).

Based on the large body of safety data from SLE patients treated with belimumab and/or the mechanism of action of belimumab as a B cell immunosuppressant, anticipated potential risks of belimumab treatment in vasculitis patents include serious infusion and hypersensitivity reactions, infections, depression-related events, and malignancy. These risks are briefly reviewed here and are detailed more fully in the belimumab Investigator's Brochure. Both investigators and subjects will be appropriately informed regarding these risks. It is noted that because of the older patient population affected by this disease, the average age of subjects anticipated to participate in this study will be older than the average age of the SLE population studied to date (mean age of ~53 years at the time of diagnosis in vasculitis (Stone et al, 2010) compared with an average age of ~38 years in controlled Phase 3 studies of belimumab in SLE). As such, patients with vasculitis may be at a greater risk for infection than the SLE patients; however, the increased monitoring for infections by both the DMC (described above) and recommended to investigators (see below) will help to ensure subject safety through timely detection, treatment and reporting of infections.

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

In order to ensure subject safety with respect to infusion and hypersensitivity reactions, the protocol excludes patients with known history of allergic reactions to human or murine proteins or monoclonal antibodies. There is currently insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions to belimumab. The protocol recommends that based on clinical judgment, premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion. Antihistamine H2-receptor antagonists (eg, ranitidine) are also permitted. Belimumab/placebo will be administered by investigators/site personnel prepared to manage infusion reactions and anaphylaxis. The infusion rate may be slowed or interrupted if the subject develops an infusion reaction. Investigators/site personnel should be aware of the risk of hypersensitivity reactions, which may present as infusion reaction, and monitor subjects

closely. In the event of a serious reaction, belimumab/placebo administration must be discontinued immediately and the appropriate medical therapy administered. Per protocol, subjects are to remain under clinical supervision for 3 hours after completion of the first 2 infusions in the double-blind treatment phase and the open-label extension. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing for any untoward reactions. Beyond the first 2 infusions, subjects should be monitored during and for an appropriate period of time after infusion according to study sites' guidelines or standard operating procedure for IV infusions. Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

The protocol recommends that subjects with persistent or worsening disease should receive appropriate rescue therapy in accordance with standard clinical practice, but if exceeding what is allowed per protocol, treatment with study agent (ie, belimumab or placebo) will be discontinued and the subject will be considered as having relapsed for the primary analysis. The list of prohibited medications that results in the subjects being considered as relapsed for the primary endpoint (Protocol Section 5.5.2.1), was developed because the need for the use of these agents (eg, RTX or CYC) is indicative of treatment failure (ie, disease relapse).

Moreover, concomitant use of such medications (eg, high-dose steroids) can be associated both with potent disease-modifying activity and/or significant toxicity that may introduce

bias and confound interpretation of results. As such, no subject will be denied appropriate medical care for their condition due to their participation in this clinical study.

In addition, the Sponsor notes that although this is a placebo controlled trial, the sponsor does not consider that placebo patients are at undue risk because all subjects in both the placebo group and the belimumab group will receive standard of care maintenance therapies for vasculitis (ie, azathioprine or methotrexate) and, if needed, subjects will receive appropriate rescue therapy in accordance with standard clinical practice as described above.

Risk:Benefit Conclusions

In summary, the proposed Phase 3 study is a superiority study evaluating the safety and efficacy of belimumab for the maintenance of disease remission in patients with a clinical diagnosis of Wegener's granulomatosis or microscopic polyangiitis. The risk:benefit profile of 10 mg/kg IV belimumab in patients with active, autoantibody-positive SLE was demonstrated to be positive in the two Phase 3 SLE studies, thereby supporting its approval in Canada, the US, and the EU. Belimumab has already been shown to be effective in treating patients with active, autoantibody-positive SLE, a B cell mediated autoimmune disease. Like SLE, WG and MPA are also B cell mediated autoimmune diseases in which autoantibodies (in this case, against neutrophil components), are considered to be pathogenic (Popa et al, 1999). In each of these diseases, the general purpose of the therapy is similar – reducing disease activity by down regulating B cells (including autoreactive B cells) and reducing the level autoantibodies produced by those autoreactive B cell clones. Down regulating B cell numbers may also reduce inflammatory processes because of the role of B cells in antigen presentation. A

limited amount of data from the IV Phase 3 studies suggests that belimumab may reduce vasculitic symptoms.

There are potential risks associated with belimumab treatment including serious infusion and hypersensitivity reactions, infections, depression-related events, and malignancy; however, in view of the serious and potentially life threatening nature of disease flares in WG and MPA, it is believed that the overall risk:benefit analysis for belimumab in the maintenance of remission in WG and MPA is favorable, especially in view of the nature of the trial as a superiority trial over a current standard of care regimen.

Sub-Appendix 1   ANCA-Associated Vasculitis Standard of Care Letter from Key Opinion Leader

**HUMAN
GENOME
SCIENCES** Human Genome Sciences, Inc.
14200 Shady Grove Road | Rockville, MD 20850

12th June 2012

RE: Clinical Protocol HGS1006-C1100 (EudraCT Number: 2011-004569-33)

Dear Sir or Madam:

This letter is in reference to Protocol HGS1006-C1100 entitled, "A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis", being conducted by Human Genome Sciences, Inc (HGS).

I confirm that the standard of care regimens proposed for use as induction therapy prior to this study, and as maintenance therapy during this study, as noted below are consistent with the current standard of care therapies being used in clinical practice for the treatment of adults with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides, specifically Wegener's granulomatosis (granulomatosis with polyangiitis) and microscopic polyangiitis.

Induction

Induction regimens that are permitted to be used prior to participation in this study (see protocol Section 3.1 for more detail) include:

1. A single course rituximab (RTX) administered at a dose of 375 mg /m^2/week for 4 weeks plus high dose corticosteroids (HDCS) OR

2. Cyclophosphamide 2mg/kg/day orally plus HDCS OR

3. Cyclophosphamide 3 IV pulses of 15 mg/kg given 2 weeks apart followed by pulses of 15 mg/kg every 3 weeks plus HDCS.

The recommended HDCS regimen with any of the above induction therapies is: methylprednisolone pulses of up to 1000 mg IV each for 1-3 days, followed by 1 mg/kg/day not to exceed 80 mg/day and tapered as clinically appropriate to reach < 10 mg/day.

To be enrolled, remission must be achieved no more than 26 weeks after the first dose of induction therapy as described above (see Protocol Section 4.1, Inclusion Criterion 5).

Maintenance

The maintenance regimen to be used during the proposed study (belimumab/placebo + azathioprine) must start no more than 2 weeks after confirmation of remission (see Protocol Section 4.1, Inclusion Criterion 5 and Section 5.5.3 for more detail). Azathioprine should be given at a target dose of 2 mg/kg/day (not to exceed 200 mg/day). Azathioprine will be initiated at any time following confirmation of remission up to and including Day 0 (time of first dose of belimumab/placebo) at a dose of 50 mg/day and increased by no more than 50 mg/day every week until the target dose is achieved.

Subjects naïve to azathioprine who develop Grade 3 or 4 leukopenia or thrombocytopenia, AST or ALT >2 times ULN, or a several gastrointestinal hypersensitivity reaction, characterized by severe nausea and vomiting, following initiation of azathioprine will be permitted to reduce the dose to no less than 1 mg/kg/day. If the subjects continues to experience toxicities described above a switch to methotrexate at doses of up to 25 mg/week as an alternative to azathioprine will be permitted.

The use of stable baseline dose regimens of corticosteroids (< 10 mg/day prednisone or equivalent) are permitted over the course of the trial.

I agree that these regimens are appropriate for use in this international clinical study.

Thank you for your consideration.

Sincerely,

PPD

PPD MD FRCP

Consultant in Nephrology & Vasculitis

PPD