CLINICAL PROTOCOL HGS1006-C1124

Protocol Amendment: 05
Date: 25 May 2022

TITLE OF STUDY:

A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)

STUDY SPONSOR:

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Revision Chronology for HGS1006-C1124 (BEL116543)

Document Identifier	Date	Document*
Global	14 August 2012	Original
Global	01 November 2012	Amendment No. 01
Local 2013N183013_00	10 December 2013	Local Addendum No. 01 for Sweden
Global 2017N316452_00	19 June 2017	Amendment No. 02
Global 2017N316452_01	12 March 2018	Amendment No. 03
Global 2017N316452_02	25 Nov 2020	Amendment No. 04
Global TMF-14148167	25 May 2022	Amendment No. 05

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

Milestones

Milestone	Planned Date
Registration in the EU PAS register	16 October 2013
Start of data collection	February 2013
End of data collection	2025
Interim Report 1	28 February 2014
Interim Report 2	28 February 2015
Interim Report 3	28 February 2016
Interim Report 4	28 February 2017
Interim Report 5	28 February 2018
Interim Report 6	28 February 2019
Interim Report 7	28 February 2020
Interim Report 8	28 February 2021
Interim Report 9	28 February 2022
Interim Report 10	28 February 2023
Interim Report 11	28 February 2024
Interim Report 12	28 February 2025
Final Report	28 February 2026

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 guidelines for Good Pharmacoepidemiology Practices (GPP) as defined by the International Society of Pharmacoepidemology (ISPE) all applicable national, state, and local regulations, as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) and any other institutional requirements.

Principal Investigator:

Signature *Date (dd mmm yy)*

Name (please type or print)

Institution

Address (must include country name)

Study Synopsis

Title of the Study: A 5-Year Observational Prospective Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)

Clinical Development Phase: 4

Objectives:

Primary Objective

To evaluate the incidence of the following adverse events of special interest (AESI) over 5 years in adults with active autoantibody-positive systemic lupus erythematosus (SLE) who are treated with or without BENLYSTA:

- Malignancies (excluding non-melanoma skin cancers)
- Mortality
- Opportunistic infections and other infections of interest (Appendix 1)
- Non-melanoma skin cancers (NMSC)
- Selected serious psychiatric events (Appendix 2)
- Serious infections

Other Objectives

To evaluate the following effectiveness measures in adults with active autoantibody-positive SLE who are treated with or without BENLYSTA:

- Organ damage as assessed by SLICC/ACR Damage Index (Appendix 5)
- Concomitant SLE medications including steroids
- Hospitalizations

Inclusion Criteria:

Patients enrolled in the registry must meet the following inclusion criteria:

1. Males or females age 18 or older.
2. Have a clinical diagnosis of active SLE.
3. Current or history of autoantibody-positive SLE.
4. Must be treated with SLE therapy including BENLYSTA and/or immunosuppressants (eg, azathioprine, methotrexate, cyclophosphamide, mycophenolate, and biologics).
5. Have the ability to understand the requirements of the study, provide written informed consent, including consent for the use and disclosure of research-related health information, and comply with the study data collection procedures.

Exclusion Criteria:

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

1. Treatment with an investigational drug within one year of enrollment. Investigational drug applies to any drug not approved for sale in the country it is being used.
2. Currently enrolled in a placebo-controlled BENLYSTA (belimumab) clinical trial or a continuation protocol where belimumab is used as an investigational agent.
3. Patients who have a history of BENLYSTA exposure, but are not currently receiving BENLYSTA.
4. Patients only receiving an anti-malarial for SLE.
5. Patients only receiving steroids for SLE.

Study Design:

This is a multi-center, prospective, observational cohort study to evaluate the incidence of adverse events of special interest (AESI) and effectiveness in patients with active, autoantibody-positive SLE treated with and without BENLYSTA. BENLYSTA refers to any commercially available formulation of belimumab. BENLYSTA formulation, intravenous (IV) or subcutaneous (SC), will be recorded for each patient in the protocol database. Patients will receive BENLYSTA at the discretion of their physician. All treatment decisions are at the discretion of the patient and their healthcare provider and are not mandated by study design or protocol. All assessments are intended to be performed at the time of clinical encounters, per routine care. Patients will be enrolled into 1 of 2 cohorts, those who, at baseline, are receiving or initiating BENLYSTA (BENLYSTA cohort) or are not receiving BENLYSTA (comparison cohort). BENLYSTA or comparison cohort patients may be either treatment initiators or current users. Treatment initiators are defined as those patients who have initiated immunosuppressants and/or BENLYSTA in the last 2 months, while the current users are those who have received immunosuppressants and/or BENLYSTA for ≥2 months at the time of entry into the registry. The study will enroll approximately 3,000 patients, approximately 2,000 in the BENLYSTA cohort and 1,000 in the comparison cohort. Enrollment is expected to occur primarily in the US, Canada, and Europe. Each patient will be followed for 5 years contributing a total of approximately 7,773 patient years in the BENLYSTA cohort and 3,886 patient years in the comparison cohort, respectively, assuming a 10% annual patient drop-out rate and not accounting for crossover.

Data will be collected at enrollment and at approximately 6 month intervals for 5 years (60 months). All patients will be assessed for AESI including serious infections, opportunistic infections and other infections of interest, malignancies (including NMSC), selected serious psychiatric events and mortality. Organ damage as assessed by SLICC/ACR Damage Index (SDI), concomitant SLE medications including steroids, demography (eg, age, gender, race/ethnicity; where allowed by local regulation), smoking history, alcohol use,

hospitalizations, and disease activity of SLE will also be evaluated in all patients at defined visits (see Table 6-1). Adverse events not collected in this study should be reported in accordance with the laws and regulations for marketed products in the country in which the event occurred.

Primary Endpoints:

Incidence of the following adverse events of special interest (AESI):

- Malignancies (excluding non-melanoma skin cancers)
- Mortality
- Opportunistic infections and other infections of interest (Appendix 1)
- Non-melanoma skin cancers (NMSC)
- Selected serious psychiatric events (Appendix 2)
- Serious infections

Effectiveness Endpoints:

- Organ damage as assessed by SLICC/ACR Damage Index (Appendix 5)
- Concomitant SLE medications including steroids
- Hospitalizations

Sample Size Consideration:

This registry will enroll approximately 3,000 patients, approximately 2,000 receiving or initiating BENLYSTA plus standard of care (BENLYSTA cohort) and 1,000 standard of care only (comparison cohort). Each patient will be followed for 5 years, contributing a total of approximately 7,773 patient years in the BENLYSTA cohort and 3,886 patient years in the comparison cohort, respectively), assuming a 10% annual patient drop-out rate and not accounting for crossover.

The registry will allow the difference in mortality rate in the BENLYSTA cohort and comparison cohort to be established with a 95% CI of +/-0.32 per 100-subject years, based on an estimated mortality rate of 0.68 per 100-subject years in both treatment groups (Table 1). The estimated mortality rate was based on the mortality rate in the pooled IV primary safety database in SLE subjects derived from 3 randomized, double-blind, IV placebo-controlled trials, referred to as IV SLE Controlled, Repeat Dose (CRD) studies (ie, integrated database of LBSL02 [placebo-controlled treatment phase only], HGS1006-C1056, and HGS1006-C1057) for all subjects (IV belimumab and placebo) adjusted for subject years. The precision of the rates of the AESI are provided in the table below:

Table 1 Precision of differences in AE rates estimated from a total of 7,773 patient years in the BENLYSTA cohort and 3,886 patient years in the comparison cohort, respectively

Adverse Events	Reference Rate[1] (per 100-patient years)	95% Confidence Interval for difference in AE rates[2] (per 100-patient years)
All deaths	0.68	±0.32
Serious infection	5.80	±0.93
Opportunistic infection	0.136	±0.14
Malignancy excl. NMSC	0.226	±0.19
NMSC	0.226	±0.19
Selected serious psychiatric events	0.410	±0.25

[1] The reference AE rates were based on the AE rates in the pooled IV primary safety database derived from the IV SLE CRD studies (LBSL02, HGS1006-C1056, HGS1006-C1057) and adjusted for subject years.

[2] Assuming that the AE rates in BENLYSTA and the control groups were the same as the reference rate.

Analysis of Primary Endpoints:

In addition to analyses that consider initial treatment group (BENLYSTA cohort vs comparison cohort), analyses that specifically account for changes in therapy (in either group) by considering a variety of risk windows will be employed. These analyses will attribute events to BENLYSTA treatment if they occur within the designated risk windows for BENLYSTA exposure and to comparison treatment otherwise. These analyses will allow for a registry patient to contribute person-time to both BENLYSTA treatment, and comparison treatment and as a result, will specifically account for treatment switching to BENLYSTA or from BENLYSTA. Switching between BENLYSTA and comparison treatment will be taken into account in a number of ways in the analysis and will be further defined within the statistical analysis plan. No new analyses for changing between BENLYSTA formulation or stratifying by BENLYSTA formulation are planned. Planned analyses are outlined below; all analyses will be detailed in the statistical analysis plan.

- Analysis by initial treatment group of rate per person years of observation time.
- Analysis by initial treatment group of rate per person years of exposure where BENLYSTA exposure ends 14 weeks (approximately 5 half-lives) after cessation of treatment.
- For serious psychiatric events, BENLYSTA exposure is all time on treatment with BENLYSTA ending 14 weeks (approximately 5 half-lives) after cessation of treatment, with all remaining treatment time attributed to the comparison cohort.
- For serious infections, opportunistic infections and other infections of interest, BENLYSTA exposure is all time on treatment with BENLYSTA ending 6 months after cessation of treatment, with all remaining treatment time attributed to the comparison cohort.
- For NMSC and malignancies excluding NMSC, analysis will be performed where all events will be attributed to BENLYSTA if the patient was ever exposed to BENLYSTA treatment prior to the event and attributed to the comparison cohort otherwise (ie, once exposed, always at risk).
- Mortality will be analyzed applying all the above-mentioned risk windows (eg, 14 weeks, 6 months, and ever-exposed).
- Other risk windows (including risk windows for comparison treatment) may also be assessed and defined in the statistical analysis plan.

Additional safety analysis will be performed comparing BENLYSTA treatment initiators with patients from the comparison cohort that start or switch an immunosuppressant and that have comparable background medication and treatment history. Subgroup analysis will be performed that will include but not be limited to analysis of patients with positive anti-dsDNA and low complement at baseline, patients with SLEDAI 2000 score at baseline (<10 vs ≥10), SDI (0 vs ≥1), steroid use (yes vs no; ≤7.5 mg/day vs >7.5 mg/day), immunosuppressant use (yes vs no; mycophenolate vs immunosuppressant other than mycophenolate), region (US/Canada vs Europe vs other), and race (black race vs other). Safety analyses will be adjusted for potential confounding factors (Appendix 7) through propensity score methods or other appropriate statistical methods. No new analyses for changing between BENLYSTA formulation or stratifying by BENLYSTA formulation are planned. Further details of the safety analyses will be described in the statistical analysis plan.

Analysis of Effectiveness Endpoints:

For any effectiveness endpoint analyses performed, methods to reduce the potential impact of confounding may be employed. These methods could include subgroup analysis, modeling adjusting for baseline and/or other confounding variables, or patient matching techniques like propensity score analysis. Furthermore, analyses considering changes in BENLYSTA use over time (eg, on or off treatment, but not changes between BENLYSTA formulations) in order to assess BENLYSTA effectiveness, as well as evaluate how these endpoints vary in response to BENLYSTA treatment will be assessed and further explored as appropriate. These analyses will be described in the statistical analysis plan.

Study Calendar:

See Table 6-1 for data collection time points.

Table of Contents

List of Tables

List of Abbreviations

ACR	American College of Rheumatology
AE	adverse Event
AESI	adverse Events of Special Interest
BAFF	B cell activating factor belonging to the TNF family
BCG	Bacillus Calmette-Guérin
BLyS	B lymphocyte stimulator
CI	Confidence Interval
CMV	cytomegalovirus
CRD	controlled repeat dose
CRF	case report form
eCRF	electronic case report form
EDC	electronic data capture
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
GSK	GlaxoSmithKline
HGS	Human Genome Sciences
HIV	human immunodeficiency virus
HR	hazard ratio
HPV	human papillomavirus
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Reports
IEC	Independent Ethics Committee
IPSE	International Society of Pharmacoepidemology
IRB	Institutional Review Board
IV	intravenous
NHL	non-Hodgkin's lymphoma
NMSC	non-melanoma skin cancer
PML	Progressive multifocal leukoencephalopathy
PSRHQ	possible suicidality-related history questionnaire
PSRQ	possible suicidality-related questionnaire
SABLE	Safety And effectiveness of Belimumab in Systemic Lupus Erythematosus Registry
SAC	Scientific Advisory Committee
SAE	serious adverse event
SDI	SLICC/ACR Damage Index
SELENA	Safety of Estrogen in Lupus National Assessment trial
SIR	Standardized Incidence Ratio
SLE	systemic lupus erythematosus
SLEDAI 2000	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
TB	tuberculosis
TNF	tumor necrosis factor

US	United States of America
UTI	urinary tract infection
WBC	white blood cell count

1 Background

1.1 Disease Background Relevant to the Registry

SLE is a chronic debilitating autoimmune disease that primarily affects young women of childbearing age, although men, children and teenagers also can develop lupus. SLE is characterized by the presence of autoreactive B cells resulting in elevated levels of autoantibodies, which directly damage the body's cells and tissues or form immune complexes which cause inflammation and tissue damage. A range of organ systems may be involved simultaneously or sequentially. The manifestations of lupus include arthritis, pleuritis, pericarditis, stroke, seizure, nephritis, vasculitis, anemia, thrombocytopenia, alopecia, photosensitivity, and malar rash. Over time, patients with lupus accrue irreversible organ damage which contributes to an increased mortality rate in these patients. Despite advances over the past 40 years in both diagnosis and treatment, patients with SLE have a 2 - 5-fold greater risk of mortality.

SLE most often develops between the ages of 15 – 44 with an insidious onset (Danchenko et al, 2006). In the US, the estimated average of the reported prevalence is approximately 10 cases per 10,000 persons, representing about 300,000 patients, and the incidence has increased 2.5-fold between 1950 and 1979 (Uramoto et al, 1999; Somers et al, 2007; Balluz et al, 2001; Naleway et al, 2005; Ward, 2004; Helmick et al, 2008). In the European Union, an estimated overall average of the reported prevalence is 4 to 5 cases per 10,000 persons (Alamanos et al, 2003; Benucci et al, 2005; Eilertsen et al, 2006; Gourley et al, 1997; Govoni et al, 2006; Gudmundson et al, 1990; Hopkinson et al, 1993; Johnson et al, 1995; Lopez et al, 2003; Nightingale et al, 2007; Nossent, 2001; Piette et al, 2004; Samanta et al, 1992; Stahl-Hallengren et al, 2000; Voss et al, 1998). Recent studies by Bernatsky et al, have emphasized the increased risk of mortality in SLE and have provided data comparing all cause and disease-specific relative mortality across groups characterized by age, sex, SLE duration, calendar-year period, geographic location, and race (Bernatsky et al, 2006). A 2.4-fold greater risk of mortality (95% CI 2.3–2.5) was identified in SLE compared with the general population and there was an increased risk of death due to cardiovascular causes, malignancy, infections, and renal disease.

In an attempt to answer the question as to whether patients with SLE have an increased risk of malignancy in comparison to the general population, several large studies have recently been conducted. In the Swedish cohort of patients with SLE, Bjornadal et al used hospital discharge data to demonstrate an increased relative risk of any malignancy in SLE patients that was 25% higher among SLE patients compared to the general population. Of note, this finding was driven primarily by the higher incidence of non-Hodgkins lymphoma (NHL) in the SLE population which had a relative risk that was 2.86-fold higher (95% CI 1.96, 4.04) than that of the general population. These findings have been subsequently confirmed by the Systemic Lupus International Collaborating Clinics research group (SLICC) in a larger international multi-center cohort study. Using Standardized Incidence Ratio (SIR) estimates, a small increase in all malignancies combined was observed (SIR, 1.15, 95% CI 1.05, 1.27) for SLE compared to that expected for the general population based on data from regional cancer registry linkages

(Bernatsky et al, 2005). Similarly, the increased risk for NHL was also demonstrated (SIR, 3.64, 95% CI 2.63, 4.93) in the SLE population compared to the general population. Unfortunately, no investigations have been able to establish the reason for the close association between SLE and malignancy. Potential considerations in this regard include abnormal immune activity early in the course of the disease, as well as cumulative exposure to immunosuppressive medications. In the SLICC international multi-center cohort study, the adjusted Hazard Ratio (HR) for overall risk of malignancy after administration of any immunosuppressive drug was 0.82 (95% CI 0.50 1.36). However, when specifically considering hematological malignancies (Bernatsky et al, 2009), there was a suggestion of an increased risk after immunosuppressive drug exposures particularly when the medication exposures were lagged by a period of 5 years (adjusted HR 2.29, 95% CI 1.02-5.15).

Infections are responsible for morbidity and mortality in 25-50% of SLE patients; they are the primary cause of death in SLE patients in developing countries (Alarcón et al, 2001; Cervera et al, 1999 and Alarcón, 2006) In a multi-center European study in which 1,000 SLE patients were followed for more than 5 years, infections and disease activity were found to be responsible for more than half of all deaths. Moreover, patients with SLE have higher rates of infections and poorer outcomes compared to the general population (Doria et al, 2008; Petri, 1998). The microorganisms responsible for the overwhelming majority of infections in patients with SLE are bacteria. However, there are many reports of infections occurring in patients with SLE with various outcomes as a consequence of other microorganisms. The increased susceptibility to infections may be multifactorial. Disease activity has been shown to be an independent risk factor for the occurrence of infections (Petri et al, 1992; Zonana-Nacach et al, 2001) presumably because of the abnormal cellular function and complement abnormalities that are more pronounced in the affected patients. The use of corticosteroids and other immunosuppressive medications has also been associated with the increased occurrence of infections in SLE (Gladman et al, 2002; Noel et al, 2001 and Petri et al, 1992). Consequently, the possibility exists that an increased occurrence of infections may occur as a consequence of cytokine suppression, resulting in multiple cellular functional abnormalities (Boumpas et al, 1993).

Neuropsychiatric events are well recognized in the SLE population, with a wide incidence range. In an international inception cohort study (Hanly, 2007), neuropsychiatric events occurred in 28% of subjects near the time of SLE diagnosis, and the incidence of mood disorders attributed to SLE ranged from 4% to 13% depending on the attribution model used. Another study (Bachen et al, 2009) found the prevalence rates of many psychiatric disorders (major depressive disorder, bipolar disorder, panic disorder, etc.) were significantly higher in patients with SLE than the general population. The rate of major depression reported in the literature for patients with SLE ranges from 22.5%-39.1% (Nery et al, 2007; Brey et al, 2002; Ainiala et al, 2001). Severe depression requiring hospitalization was found to be 0.26% (14/5371 SLE patients in a Swedish cohort followed from 1973 to 2004) (Sundquist et al, 2008). Chronic physical illness is also an important risk factor for suicide (Karassa et al, 2003). Patients with SLE are at almost 5 times greater risk for suicide than expected (Harris et al, 1994). Suicide attempts among SLE patients was 5/300 SLE patients who visited a UK Rheumatology Clinic

over a 20-year period (1979-1999) (Karassa et al, 2003) with deaths attributed to suicide ranging from 0.23-0.95% (Mok et al, 2008; Nossent et al, 2001; Karassa et al, 2003).

1.2 BENLYSTA Background Relevant to the Registry

BENLYSTA (belimumab) is a recombinant human IgG1λ monoclonal antibody that binds to soluble human B-lymphocyte stimulator (BLyS; also known as B cell activating factor belonging to the tumor necrosis factor (TNF) family [BAFF] and TNFSF13B) and inhibits its biological activity (Baker, 2003).

The primary safety population, derived from 3 randomized, double-blind, IV placebo-controlled trials, referred to as IV SLE Controlled, Repeat Dose (CRD) studies, included safety data from the double-blind portion of the two phase 3 studies discussed above (HGS1006-C1056 and HGS1006-C1057) as well as the double-blind portion of a Phase 2 study (LBSL02) in 449 subjects with SLE. A summary of adverse events of special interest in this dataset, the same as that to be evaluated in this registry, is provided in Table 1-1. Additional information is provided in the Package Insert/Summary of Product Characteristics.

Table 1-1 Adverse Events of Special Interest (IV SLE CRD) [1]

	Placebo N = 675	1 mg/kg N = 673	10 mg/kg N = 674
All Cause Mortality			
Deaths	3 (0.4%)	5 (0.7%)	6 (0.9%)
Infections and Infestations			
At least 1 Infection AE	455 (67.4%)	484 (71.9%)	477 (70.8%)
At least 1 serious infection AE	37 (5.5%)	48 (7.1%)	36 (5.3%)
Opportunistic infections	-	1 (0.1%)	2 (0.3%)
Malignancies			
Malignancies (all)	3 (0.4%)	4 (0.6%)	3 (0.4%)
Non-melanoma skin cancers (NMSC)	1 (0.1%)	1 (0.1%)	3 (0.4%)
Malignancies excluding NMSC	2 (0.3%)	3 (0.4%)	-
Hematological malignancies	-	-	-
Psychiatric Disorders			
Psychiatric Disorders (SOC)	84 (12.4%)	108 (16.0%)	107 (15.9%)
Serious	3 (0.4%)	4 (0.6%)	8 (1.2%)
Depression/Self-Injury	34 (5.0%)	44 (6.5%)	41 (6.1%)
Serious	2 (0.3%)	3 (0.4%)	4 (0.6%)
Suicide	-	1 (0.1%)	1 (0.1%)

[1] Final integrated safety data from 3 IV SLE CRD trials: LBSL02, HGS1006-C1056 and HGS1006-C1057.

With respect to mortality, 14 deaths occurred during the double-blind periods of these 3 randomized, placebo-controlled SLE trials: 3 (0.4%) in the placebo group, 5 (0.7%) in the

1 mg/kg group and 6 (0.9%) in the 10 mg/kg group. An additional death due to respiratory arrest was reported more than 3 months after the subject's participation in a Phase 3 study (1 mg/kg group). No single cause of death predominated. Etiologies included infection, cardiovascular disease, and suicide. When all IV belimumab SLE studies are considered as of 15 May 2011, including long-term studies, the mortality rate per 100 patient-years was 0.56 and 0.43 in subjects receiving belimumab and placebo, respectively.

In total, 10 malignant neoplasms, 5 solid organ malignancies and 5 non-melanoma skin cancers, were reported in the primary safety population trials. The 5 solid organ malignancies were:

- Stomach carcinoid (placebo, Day 202)
- Breast cancer (placebo, 2 months after last dose)
- Breast cancer (1 mg/kg, Day 102)
- Cervical cancer (1 mg/kg, Stage 0 in situ, 1.2 years)
- Ovarian cancer (1 mg/kg, Day 21)

The ovarian cancer ultimately resulted in the death of the patient. There were 5 non-melanoma skin cancers: 2 basal cell carcinoma and 3 squamous cell carcinoma of the skin (1 in the placebo group, 1 in the 1 mg/kg group, 3 in the 10 mg/kg belimumab group). No solid organ malignancies occurred in the 10 mg/kg group. No hematological malignancies were reported in the primary safety population. The rate of malignancy, excluding non-melanoma skin cancers, across the entire SLE experience as of 15 May 2011 was compared with the malignancy rate in SLE patients reported in the literature (Bernatsky et al, 2005). Excluding non-melanoma skin cancers is appropriate given that it is known that these are underreported in observational studies compared with prospective clinical trials. The malignancy rate per 100 patient-years with belimumab is 0.52 (95% CI: 0.34, 0.77) compared with a background rate in SLE subjects of 0.53 (95% CI: 0.48, 0.59) (Bernatsky et al, 2005). No pattern of malignancies or an increase in any particular type of malignancy was identified in subjects receiving belimumab.

As with other immunomodulating agents, the mechanism of action of belimumab may increase the risk for the development of infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant therapy, including belimumab. Serious infections occurred in 5% to 7% of subjects across the treatment groups in the primary safety population. The top 5 most frequent serious infections ($\geq$ 3 subjects in any treatment group) were pneumonia, UTI, cellulitis, bronchitis, herpes zoster, and pyelonephritis; these events generally occurred at similar rates between the placebo and the belimumab groups. There was no apparent treatment effect or belimumab dose relationship in the incidence of the individual serious infections that occurred most frequently. One placebo and 3 belimumab infectious deaths were related to sepsis, while 1 belimumab 10 mg/kg death was related to infectious diarrhea. Each of these subjects was taking a concomitant steroid and at least 1 other immunosuppressant or antimalarial drug. The 2 opportunistic infections in the 10 mg/kg group included disseminated cytomegalovirus (CMV) infection on Day 62 that resolved after 52 days and Acinetobacter bacteremia on Day 15 that resolved after 28 days. A third potential

opportunistic infection occurred in a subject receiving 1 mg/kg belimumab (preferred term: pneumonia bacterial infection; verbatim: atypical pneumonia, Acinetobacter lwolfii) on Day 1 of study so is unlikely to be causally related to belimumab. The infection was treated with antibiotics, resolved after 11 days, and was considered not related to belimumab; belimumab treatment continued. Overall, in the long-term uncontrolled SLE experience, the incidence of infections, including severe and serious infections, remained stable or declined over time. In terms of potentially opportunistic infections or other infections of interest in the long-term experience as of 09 June 2010, 1 subject had coccidioidomycosis in Year 4 of exposure, and another developed a fatal CMV pneumonia also in Year 4 of exposure. Three cases of mycobacterial infections (1 latent pulmonary tuberculosis TB [serious], 1 extra pulmonary TB [serious], and 1 atypical mycobacterial infection [non-serious]), which had not previously been observed in belimumab-treated SLE subjects have been reported. Another case of non-serious latent pulmonary TB has also been identified. All mycobacterial infections were reported in subjects from countries where TB is endemic. Given that SLE patients are known to be at higher risk for tuberculosis (Erdozain et al, 2006), it is not believed that belimumab treatment increases the risk of tuberculosis.

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 patient presenting with new-onset or deteriorating neurological signs and symptoms. The patient should be referred to a neurologist or other appropriate specialist for evaluation and if PML is confirmed, consideration should be given to stopping immunosuppressant therapy, including belimumab.

Psychiatric events were reported more frequently with belimumab (16%) than with placebo (12%), driven primarily by mild/moderate events of insomnia, depression, and anxiety. Serious psychiatric events also were reported at a slightly higher proportion (0.8% with belimumab compared with 0.4% with placebo), although the numbers of events were small. There were 2 completed suicides in belimumab-treated subjects in the primary safety population. A composite analysis of depression and self-injury/suicide events was performed that showed rates ranging from 5-6% across groups, and serious events were reported in 0.3%, 0.4% and 0.6% of subjects in the placebo, 1 mg/kg and 10 mg/kg groups, respectively. The majority of subjects who reported serious depression or suicidal behavior had a history of depression or other serious psychiatric disorders and most were receiving psychoactive medications; in addition, these events were not judged to be related to belimumab treatment, nor did they (with the exception of the completed suicides) lead to discontinuation of belimumab.

Although not being evaluated as part of this long-term observational registry, infusion and hypersensitivity reactions, including anaphylaxis and death, have been reported in association with belimumab. Delay in the onset of acute hypersensitivity reactions has been observed. Limited data suggest that patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. Belimumab should be administered by healthcare providers prepared to manage infusion reactions and anaphylaxis. More information about this risk can be found in the package insert/summary of product characteristics.

Clinical studies of SC belimumab have demonstrated a safety profile consistent with the established safety profile of IV belimumab. The rates of adverse events of special interest, including mortality, (primary endpoints) are not reasonably expected to be affected by route of administration [Stohl, 2017]. Patients treated with either formulation are therefore eligible to participate in this registry.

1.3 Rationale for the Registry

Conservative therapy that is used for non-organ threatening SLE disease may include salicylates, nonsteroidal anti-inflammatory drugs, anti-malarials, and low dose corticosteroids. Therapies for more severe or organ threatening disease may include high dose corticosteroids, methotrexate, leflunomide, azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, rituximab, anti-TNFs, intravenous immune globulin, and plasmapheresis used in combination with or without medications used for milder disease. While there is concern that immunosuppressive medications used in the treatment of SLE are associated with malignancy and with increased occurrence of infection, as well as other potentially serious toxicities (eg, osteoporosis, osteonecrosis, metabolic abnormalities), the use of immunosuppressant medications in SLE may be necessary to reduce the likelihood of disease-related morbidity and death as well as to delay and prevent long term damage resulting from some treatments (Urowitz et al, 2012).

While substantial information exists about the safety of BENLYSTA from clinical trials, it is important to evaluate the safety of BENLYSTA in real world practice settings over a prolonged period of time, particularly with respect to the occurrence of malignancy and serious or opportunistic infections. In order to achieve this, it is necessary to gather data on treatment, safety and effectiveness in the real world setting over an extended period that can be interpreted in the context of other patients not receiving BENLYSTA. It is important to note that differences between patients receiving and not receiving BENLYSA, other than BENLYSTA exposure, may influence the outcomes and hence confound any planned comparisons in this registry. Such factors include baseline disease activity, organ damage, other background treatment, duration of disease, etc. The key challenge in this setting is to attempt to minimize such potential confounding by selecting appropriate comparison patients as well as collating relevant information on potential confounders and making necessary adjustments in the statistical models.

The primary objective of this study is to evaluate the incidence of adverse events of special interest (AESI) over 5 years. AESI collected in this study include: serious infections, opportunistic infections and other infections of interest, malignancies (including NMSC), selected serious psychiatric events and mortality in patients with SLE being treated with and without BENLYSTA. Additionally, the study may also evaluate the following effectiveness measures in adults with active autoantibody-positive SLE who are treated with or without BENLYSTA: organ damage as assessed by SLICC/ACR Damage Index (SDI), concomitant SLE medications including steroids, and hospitalizations.

2 Study Design

This is a multi-center, prospective, observational cohort study to evaluate the incidence of adverse events of special interest (AESI) and effectiveness in patients with active, autoantibody-positive SLE treated with and without BENLYSTA. BENLYSTA refers to any commercially available formulation of belimumab. BENLYSTA formulation, intravenous (IV) or subcutaneous (SC), will be recorded for each patient in the protocol database. Patients will receive BENLYSTA at the discretion of their physician. All treatment decisions are at the discretion of the patient and their healthcare provider and are not mandated by study design or protocol. All assessments are intended to be performed at the time of clinical encounters, per routine care. Patients will be enrolled into 1 of 2 cohorts, those who, at baseline, are receiving or initiating BENLYSTA (BENLYSTA cohort) or are not receiving BENLYSTA (comparison cohort). BENLYSTA and comparison cohort patients may be either treatment initiators or current users. Treatment initiators are defined as those patients who have initiated immunosuppresants and/or BENLYSTA in the last 2 months, while the current users are those who have received immunosuppressants and/or BENLYSTA for ≥ 2 months at the time of entry into the registry. The study will enroll approximately 3,000 patients, approximately 2,000 in the BENLYSTA cohort and 1,000 in the comparison cohort. Enrollment is expected to occur primarily in the US, Canada, and Europe. Each patient will be followed for 5 years contributing a total of approximately 7,773 patient years in the BENLYSTA cohort and 3,886 patient years in the comparison cohort, respectively, assuming a 10% annual patient drop-out rate and not accounting for crossover.

Data will be collected at enrollment and at approximately 6 month intervals for 5 years (60 months). All patients will be assessed for AESI including serious infections, opportunistic infections and other infections of interest, malignancies (including NMSC), selected serious psychiatric events and mortality. Organ damage as assessed by SLICC/ACR Damage Index (SDI), concomitant SLE medications including steroids, hospitalizations, demography (eg, age, gender, race/ethnicity, where allowed by local regulation), smoking history, alcohol use, and SLE disease activity (as assessed by the SLEDAI 2000) will also be evaluated in all patients at defined visits (see Table 6-1). Adverse events not collected in this study should be reported in accordance with the laws and regulations for marketed products in the country in which the event occurred.

Patients who become pregnant during their participation in this registry will be encouraged to also participate in a separate pregnancy registry (if available at the time).

3 Objectives

Primary Objective:

To evaluate the incidence of the following adverse events of special interest (AESI) over 5 years in adults with active autoantibody-positive systemic lupus erythematosus (SLE) who are treated with or without BENLYSTA:

- Malignancies (excluding non-melanoma skin cancers)
- Mortality
- Opportunistic infections and other infections of interest (Appendix 1)
- Non-melanoma skin cancers (NMSC)
- Selected serious psychiatric events (Appendix 2)
- Serious infections

Other Objectives:

To evaluate the following effectiveness measures in adults with active autoantibody-positive SLE who are treated with or without BENLYSTA:

- Organ damage as assessed by SLICC/ACR Damage Index (Appendix 5)
- Concomitant SLE medications including steroids
- Hospitalizations

4 Outcome Definitions and Measures

The following outcomes will be collected in the registry:

Safety

- Malignancies (excluding NMSCs): Malignancies are cancers (excluding NMSC) that have the ability to spread to other parts of the body (metastasize) or to invade and destroy tissues and cause death.
- Mortality: Survival status will be collected at each data collection time point after enrollment. If death occurs, the cause of death will be collected.
- Opportunistic infections and other infections of interest: Opportunistic infections are a subset of infections that are caused by organisms that usually do not cause disease in immunocompetent individuals but which may cause illness, or more severe illness, when the immune system is suppressed. Since there are no general guidelines for labeling pathogens as opportunistic without considering the host's immune condition, identification of opportunistic infections in this study is based on a list of pathogens which, when present, may indicate immune suppression in a patient. These pathogens and infections in general are not observed in immunocompetent individuals and will be considered opportunistic. Pathogens and infections considered to be opportunistic include but not limited to those listed in Appendix 1. All potential opportunistic infections (and other infections of interest as noted in Appendix 1), irrespective of seriousness, will be collected.
- Non-melanoma skin cancer: NMSC is a malignant growth of the external surface or epithelial layer of the skin. NMSC most often originates from the external skin surface as a squamous cell carcinoma or a basal cell carcinoma.

- Selected serious psychiatric events: Selected serious psychiatric events suggestive of mood disorders and anxiety, as defined in Appendix 2, will be collected.
- Serious infections: Serious infections, including serious opportunistic infections, are defined as those that result in death, are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; require treatment with intravenous antimicrobials (eg, antibiotics, antifungals, antivirals); result in persistent or significant disability/incapacity; or are, based upon appropriate medical judgment, important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. All serious infections will be collected. See Section 7.1 for the definition of serious adverse events (SAEs).

Effectiveness

- Organ damage: The SDI (Appendix 5) is designed to capture items of irreversible organ damage present for at least 6 months (Gladman et al, 1996) occurring in patients with SLE regardless of exact cause. It consists of 12 organ system scales each having subscales comprised of up to 6 components.
- Concomitant SLE medications including steroids: The medications used to treat SLE (eg, immunosuppressants, anti-malarials, corticosteroids, biologics, and investigational agents for SLE) will be collected.
- Hospitalization: An inpatient hospitalization is defined as an admission for greater than 24 hours. An admission for administration of medication or for routine or planned clinical procedures should not be considered a hospitalization. Dates of hospital admission and discharge, and whether the hospitalization was SLE-related will be collected, as available.

5 Inclusion and Exclusion Criteria

5.1 Inclusion Criteria

Patients enrolled in the registry must meet the following inclusion criteria:

1. Males or females age 18 or older.
2. Have a clinical diagnosis of active SLE.
3. Current or history of autoantibody-positive SLE.
4. Must be treated with SLE therapy including BENLYSTA and/or immunosuppressants (eg, azathioprine, methotrexate, cyclophosphamide, mycophenolate, and biologics).
5. Have the ability to understand the requirements of the study, provide written informed consent, including consent for the use and disclosure of research-related health information, and comply with the study data collection procedures.

5.2 Exclusion Criteria

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

1. Treatment with an investigational drug within one year of enrollment. Investigational drug applies to any drug not approved for sale in the country it is being used.
2. Currently enrolled in a placebo-controlled BENLYSTA (belimumab) clinical trial or a continuation protocol where belimumab is used as an investigational agent.
3. Patients who have a history of BENLYSTA exposure, but are not currently receiving BENLYSTA.
4. Patients only receiving an anti-malarial for SLE.
5. Patients only receiving steroids for SLE.

6 Data Collection

6.1 Study Enrollment Evaluations

The following data will be collected at enrollment (baseline). Data collection for enrollment may be carried out over more than one clinical evaluation visit.

1. Written informed consent (including consent for the use and disclosure of research-related health information).
2. Demographics (eg, age, gender, race/ethnicity (where allowed by local regulation), smoking history, alcohol use)
3. Medical history (including SLE history). Note: To collect additional important information on potential suicidality-related events, should any of the psychiatric events marked with an asterisk in Appendix 2 be present at enrollment, the investigator should complete the Possible Suicidality-Related History Questionnaire (PSRHQ) eCRF (see Appendix 3).
4. Potential Confounders for Malignancies and/or Infections List (refer to Appendix 7).
5. Obtain historical and current SLE medications (immunosuppressants, antimalarials, corticosteroids and biologics). The name of the each SLE medication and start and stop dates will be recorded. In addition, for corticosteroids, the prescribed dose will be recorded. If the patient is receiving BENLYSTA, the date of first dose, and route of administration (IV or SC) will be recorded as well as name of the other SLE medications the patient was receiving at the time BENLYSTA therapy was initiated.
6. SLEDAI 2000 (see Appendix 6). To complete SLEDAI 2000, data from the following laboratory tests if available: Hematology (WBC, platelets), complement (C3, C4), anti-dsDNA, routine urinalysis, and spot urine for macroscopic/microscopic/proteinuria assessments. Note: Laboratory values should not be attributed on the SLEDAI 2000 unless laboratory values were obtained within 30 days of enrollment otherwise the laboratory values will be noted as not done.
7. SLICC/ACR Damage Index (Appendix 5).
8. Hospitalizations occurring in the previous 6 months.

9. Confirm patient meets study eligibility criteria.

6.2 On Study Evaluations

After enrollment, patients will continue to be followed regardless of changes in medication until study completion. The investigator will manage the patient in accordance with their medical judgment and standard of care. Data will be collected on patients approximately every 6 months as outlined in the study calendar (Table 6-1). Each evaluation may be conducted within 2 months (±2 months) of the scheduled data collection time point, except the last time point (Month 60), where data collection can occur up to +3 months.

The following data will be collected at each 6-month time point:

- SLICC/ACR Damage Index (Appendix 5).
- SLE medications (eg, immunosuppressants, BENLYSTA, antimalarials, corticosteroids, biologics, investigational agents for SLE). The name of each SLE medication and start and stop dates will be recorded. If a patient currently using BENLYSTA changes formulation, the original BENLYSTA record must be updated with a stop date and a new BENLYSTA record needs to be created with a start date for the new formulation. The new BENLYSTA record should also include formulation (IV or SC).
- In addition, the average daily dose of corticosteroids, in prednisone equivalents, will be recorded.
- Hospitalizations. Dates of inpatient hospital admission and discharge, and whether the hospitalization was SLE-related will be collected, as available.
- Adverse events of special interest (see Section 7.2.1). Note: In order to collect additional important information on potential suicidality-related events, should any of the events marked with an asterisk in Appendix 2 occur, the investigator will be requested to complete the Possible Suicidality-Related History Questionnaire (PSRHQ) eCRF (only the first time a serious suicidality-related event is reported and a Possible Suicidality-Related Questionnaire (PSRQ) eCRF (each time a serious suicidality-related event is reported). The PSRHQ and PSRQ are provided in Appendix 3 and Appendix 4, respectively.

6.3 Registry Completion

All patients who do not discontinue, or are not withdrawn, or are not lost to follow-up (see Section 6.4) will remain in the registry for 5 years. Record retention should occur in accordance with Section 11.6.

6.4 Discontinuation and Lost to Follow-Up

Patients will be free to withdraw from this registry at any time, for any reason. It is understood that an excessive rate of withdrawals can render the data un-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Patients will continue to be followed regardless of changes in medication until study completion. Patients may be withdrawn from this registry for any of the following reasons:

- Withdrawal of consent
- Lost to follow-up
- At the discretion of the investigator
- Patient enrolls in an interventional trial utilizing an investigational drug or a drug with the same mechanism of action as BENLYSTA
    - *Note: patients who wish to enroll in an interventional trial with a marketed drug being utilized as an investigational agent for the treatment of SLE may be able to continue in SABLE following discussion with the GSK medical monitor.*

If a patient wishes to discontinue participation in the registry, the data collection for the next study evaluation will be obtained at the time of the patient's next routinely scheduled clinical assessment. If data collection has been performed within 2 months before the discontinuation visit, it need not be repeated.

Patients will be considered lost-to-follow-up if no contact can be established by the time a patient is beyond 5 years and 3 months from their enrolment date (Day 0). Investigators or qualified designees should document attempts to re-establish contact with patients throughout the study period. If contact with a patient is re-established before the last follow-up timepoint at 60 months (-2/+3 months), follow-up should resume according to the protocol.

Table 6-1 Study calendar

	Time Points										
Data Collection [7]	**Enrollment**[1] (Day 0)	**6 months** (± 2 months)	**12 months** (± 2 months)	**18 months** (± 2 months)	**24 months** (± 2 months)	**30 months** (± 2 months)	**36 months** (± 2 months)	**42 months** (± 2 months)	**48 months** (± 2 months)	**54 months** (± 2 months)	**60 months** (-2 / +3 months) [6]
Informed Consent	x										
Demographics	x										
Medical History (including SLE history)/ General Medical Status	x				x[3]				x[3]		
Potential Confounders for Malignancies and/or Infections List	x										
Historical SLE Medications	x										
SLEDAI 2000[2]	x										
Verify Eligibility Criteria	x										
SLICC/ACR Damage Index	x	x	x	x	x	X	x	x	x	x	x
Record Current SLE Medications (including corticosteroids)[4]	x	x	x	x	x	X	x	x	x	x	x
Record Hospitalizations	x	x	x	x	x	X	x	x	x	x	x
Record AEs of Special Interest[5]		x	x	x	x	X	x	x	x	x	x

1 Data collection for enrollment may occur over more than one day.

2 Laboratory values should not be attributed on the SLEDAI 2000 unless laboratory values were obtained within 30 days of the assessment.

3 Only General Medical Status (current status of medical condition and/or medical procedure/surgery since last reported) is collected at 24 and 48 months.

4 SLE Medications include immunosuppressants, biologics, antimalarials, corticosteroids, and investigational agents for SLE. If a patient currently using BENLYSTA changes formulation, the original BENLYSTA record must be updated with a stop date and a new BENLYSTA record needs to be created with a start date for the new formulation. The new BENLYSTA record should also include formulation (IV or SC).

5 AEs of special interest for this study include mortality, serious infections, opportunistic infections and other infections of interest, selected serious psychiatric events, and malignancies (including NMSC). In order to collect additional important information on potential suicidality-related events, should any of the events marked with an asterisk in Appendix 2 occur, the investigator will be requested to complete the PSRHQ eCRF (only the first time a serious suicidality-related event is reported) and a PSRQ eCRF (each time a serious suicidality-related event is reported). The PSRHQ and PSRQ are provided in Appendix 3 and Appendix 4, respectively.

6 For the last time point (60 months), data collection is extended by an additional 1 month and therefore can occur up to 63 months after enrollment (Day 0). This is to provide sites with additional time to contact patients before declaring them as lost-to-follow-up.

[7] The data collection time intervals of 6 months ±2 months are intended to align with routine standard of care visits for SLE patients. With the exception of the last time point at 60 months (for which data collection can only be extended up to 63 months), data collection occurring outside the time window (±2 months) should be assigned to the closest time point.

7 Adverse Events

7.1 Definitions

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

SERIOUS ADVERSE EVENT – an adverse event resulting in any of the following outcomes:

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

*An inpatient hospitalization is defined as an admission and inpatient stay for at least 24 hours. A hospitalization for administration of medication, 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.

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

UNEXPECTED ADVERSE EVENT: An adverse event, the nature or severity of which is not consistent with the applicable product information (eg, package insert/summary of product characteristics for an approved product). Expected means the event has previously been observed 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.

7.2 Reporting Adverse Events

7.2.1 Adverse Events of Special Interest

The following adverse events of special interest (AESI) will be collected in this registry:

- Malignancies (excluding non-melanoma skin cancers)
- Mortality
- Opportunistic infections and other infections of interest (Appendix 1)

- Non-melanoma skin cancers (NMSC)
- Selected serious psychiatric events (Appendix 2)
- Serious infections

All AESI identified from enrollment throughout the duration of the study will be recorded on the Adverse Event Case Report Form (AE eCRF). All data fields on the AE eCRF should be completed.

7.2.2 Serious AESI and Deaths

All AESI that meet the criteria of a serious adverse event and deaths must be recorded in the SAE section of the protocol database within 24 hours of site personnel becoming aware of a SAE. In the event the protocol database cannot be accessed, the SAE Worksheet should be used and information faxed to the Drug Safety Designee. All pages of the SAE Database/Worksheet should be completed and not held until all information is available. Additional information and corrections should be added to the protocol Database/Worksheet when available.

7.2.3 Other Adverse Events

Other adverse events (including serious adverse events) not collected as AESIs in this registry should be reported in accordance with the laws and regulations for marketed products in the country where the event occurred.

7.3 Suicidality

Some autoimmune diseases have an increased risk of suicidal behavior and/or ideation (Bachen, 2009; Timonen, 2003; Stenager, 1992). In order to collect additional important information on potential suicidality-related events, should any of the events marked with an asterisk in Appendix 2 occur, the investigator will be requested to complete the Possible Suicidality Related-History Questionnaire (PSRHQ) eCRF (only the first time a serious suicidality-related event is reported) and a Possible Suicidality-Related Questionnaire (PSRQ) eCRF (each time a serious suicidality-related event is reported). The PSRHQ collects past medical history in relation to SLE-related neuropsychiatric events prior to study enrollment. The PSRQ collects other information important for evaluating suicidality-related events such as use of illicit drugs, alcohol, other stressors, family history of suicidality and other psychiatric disorders. The PSRHQ and PSRQ are provided in Appendix 3 and Appendix 4, respectively.

7.4 Investigator Evaluation of Adverse Events

The Investigator will evaluate all AESI with respect to seriousness (criteria listed in Section 7.1), severity (intensity or grade) and causality (relationship to medicinal product) according to the following guidelines:

SEVERITY:

- **Mild** - causing no limitation of usual activities.
- **Moderate** - causing some limitation of usual activities.
- **Severe** - causing inability to carry out usual activities.
- **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" in Section 7.1). The former means that the event is a potential threat to life. The latter means that the event is an immediate threat to life.

CAUSALITY

Definitely Related
- reasonable temporal relationship to medicinal product administration
- follows a known response pattern (eg, medicinal product 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.

7.5 Follow-Up of Adverse Events of Special Interest

AESI (Section 7.2.1) and Serious AESI (Section 7.2.2) that occur from study entry are followed until the final outcome is known or until the end of patient participation.

7.6 Reporting Serious Adverse Events to the Regulatory Authorities and Institutional Review Board/Ethics Committee

The Sponsor or its designee, will follow 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 serious AESI to the IRBs/IECs responsible for reviewing the study at their site, as well as the regulatory authority(ies) (if applicable).

AESI that are study endpoints (as defined in Section 7.2.1) generally will not be submitted as expedited reports to regulatory authorities or participating investigators. However, serious AESIs related to belimumab will be reported by GSK to regulatory authorities as expedited individual case safety reports (ICSRs).

8 Data Analysis

8.1 General Statistical Considerations

This registry will observe mortality and AESI as well as effectiveness outcomes on patients with diverse treatment experience both during the registry and prior to enrollment. Some patients may enter the study already receiving BENLYSTA therapy (current user) and some patients may initiate BENLYSTA therapy within the last 2 months prior to study entry (treatment initiator). During the study, some patients receiving BENLYSTA therapy may stop and potentially restart therapy, and some comparison cohort patients may elect to initiate BENLYSTA therapy at some point subsequent to enrollment. Because of these complexities, a variety of analyses will be employed, some of which consider time periods of switching on and off BENLYSTA treatment. Since the initiation of this registry, a SC formulation of belimumab has been submitted for marketing authorization. The protocol database has been modified to capture formulation of BENLYSTA but reporting and analyses will not be separated by formulation.

Patients will be considered evaluable in the BENLYSTA cohort upon receiving a single, full or partial dose administration of BENLYSTA and collection of enrollment data (Section 6.1) and at least 1 post baseline assessment (Section 6.2). Patients will be considered evaluable in the comparison cohort if there is collection of enrollment data (Section 6.1) and at least 1 post baseline assessment (Section 6.2).

8.2 Sample Size Consideration

This registry will enroll approximately 3,000 patients approximately 2,000 receiving or initiating BENLYSTA plus standard of care (BENLYSTA cohort) and 1,000 standard of care only (comparison cohort). Each patient will be followed for 5 years, contributing a total of approximately 7,773 patient years in the BENLYSTA cohort and 3,886 patient years in the

comparison cohort, respectively, assuming a 10% annual patient drop-out rate and not accounting for crossover.

The registry will allow the difference in mortality rate in the BENLYSTA cohort and comparison cohort to be established with a 95% CI of +/-0.30 per 100-subject years, based on an estimated mortality rate of 0.68 per 100-subject years in both treatment groups (Table 8-1). The estimated mortality rate was based on the mortality rate in the pooled IV primary safety database in SLE subjects derived from 3 randomized, double-blind, IV placebo-controlled trials, referred to as IV SLE CRD studies (ie, integrated database of LBSL02 [placebo-controlled treatment phase only], HGS1006-C1056, and HGS1006-C1057) for all subjects (IV belimumab and placebo) adjusted for subject years. The precision of the rates of the AESI are provided in the table below:

Table 8-1 Precision of differences in AE rates estimated from a total of 7773 patient years in the BENLYSTA cohort and 3886 patient years in the comparison cohort, respectively

Adverse Events	Reference Rate[1] (per 100-patient years)	95% Confidence Interval for difference in AE rates[2] (per 100-patient years)
All Deaths	0.68	±0.32
Serious infection	5.80	±0.93
Opportunistic infection	0.136	±0.14
Malignancy excl. NMSC	0.226	±0.19
NMSC	0.226	±0.19
Serious Psychiatric Events	0.410	±0.25

1 The reference AE rates were based on the AE rates in the pooled IV primary safety database derived from 3 IV SLE CRD studies (LBSL02, HGS1006-C1056, HGS1006-C1057) and adjusted for subject years.

2 Assuming that the AE rates in BENLYSTA and the control groups were the same as the reference rate.

8.3 Endpoints and Analysis

8.3.1 Primary Endpoints

The primary endpoints are the incidence of the following AESI:

- Malignancies (excluding NMSC)
- Mortality
- Opportunistic infections and other infections of interest (Appendix 1)
- NMSC
- Serious psychiatric events (Appendix 2)
- Serious infections

8.3.2 Analysis of Primary Endpoints

In addition to analyses that consider initial treatment group (BENLYSTA cohort vs. comparison cohort), analyses that specifically account for changes in therapy (in either group) by considering a variety of risk windows will be employed. These analyses will attribute events to BENLYSTA treatment if they occur within the designated risk windows for BENLYSTA exposure and to comparison treatment otherwise. These analyses will allow for a registry patient to contribute person-time to both BENLYSTA treatment, and comparison treatment and as a result, will specifically account for treatment switching to BENLYSTA or from BENLYSTA. Switching between BENLYSTA and comparison treatment will be taken into account in a number of ways in the analysis and will be further defined within the statistical analysis plan. No new analyses for changing between BENLYSTA formulation or stratifying by BENLYSTA formulation are planned. Planned analyses are outlined below; all analyses will be detailed in the statistical analysis plan.

- Analysis by initial treatment group of rate per person years of observation time.
- Analysis by initial treatment group of rate per person years of exposure where BENLYSTA exposure ends 14 weeks (approximately 5 half-lives) after cessation of treatment.
- For serious psychiatric events, BENLYSTA exposure is all time on treatment with BENLYSTA ending 14 weeks (approximately 5 half-lives) after cessation of treatment, with all remaining treatment time attributed to the comparison cohort.
- For serious infections, opportunistic infections and other infections of interest, BENLYSTA exposure is all time on treatment with BENLYSTA ending 6 months after cessation of treatment, with all remaining treatment time attributed to the comparison cohort.
- For NMSC and malignancies excluding NMSC, analysis will be performed where all events will be attributed to BENLYSTA if the patient was ever exposed to BENLYSTA treatment prior to the event and attributed to the comparison cohort otherwise (ie, once exposed, always at risk).
- Mortality will be analyzed applying all the above-mentioned risk windows (eg, 14 weeks, 6 months, and ever-exposed).
- Other risk windows (including risk windows for comparison treatment) may also be assessed and defined in the statistical analysis plan.

Additional safety analysis will be performed comparing BENLYSTA treatment initiators with patients from the comparison cohort that start or switch an immunosuppressant and that have comparable background medication and treatment history. Subgroup analysis will be performed that will include but not be limited to analysis of patients with positive anti-dsDNA and low complement at baseline, patients with SLEDAI 2000 score at baseline (< 10 vs ≥ 10), SDI (0 vs ≥ 1), steroid use (yes vs no; ≤ 7.5 mg/day vs > 7.5 mg/day), immunosuppressant use (yes vs no; mycophenolate vs immunosuppressant other than mycophenolate), region (US/Canada vs Europe vs other), and race (black race vs other). Safety analyses will be adjusted for potential confounding factors (Appendix 7) through propensity score methods or other appropriate statistical methods. No new analyses for changing between BENLYSTA formulation or

stratifying by BENLYSTA formulation are planned. Further details of the safety analyses will be described in the statistical analysis plan.

8.3.3 Effectiveness Endpoints and Analysis

Additional endpoints include the following:

- Organ damage as assessed by SLICC/ACR Damage Index (Appendix 5)
- Concomitant SLE medications including steroids
- Hospitalizations

For any effectiveness endpoint analyses performed, methods to reduce the potential impact of confounding may be employed. These methods could include subgroup analysis, modeling adjusting for baseline and/or other confounding variables, or patient matching techniques like propensity score analysis. Furthermore, analyses considering changes in BENLYSTA use over time (eg, on or off treatment, but not changes between BENLYSTA formulations) in order to assess BENLYSTA effectiveness, as well as evaluate how these endpoints vary in response to BENLYSTA treatment will be assessed and further explored as appropriate. These analyses will be described in the statistical analysis plan.

9 Scientific Advisory Committee (SAC)

A Scientific Advisory Committee (SAC) consisting of global clinical experts, along with GSK staff (clinical, statistics, epidemiology) will be formed. The SAC will meet as needed to review the data collected.

10 Study Limitations

This is a registry and, as such, participants are not randomized into study arms. Due to the lack of randomization, there is a significant risk of confounding (ie, imbalance in important baseline characteristics between the BENLYSTA cohort and the comparison cohort where these characteristics are also risk factors for the outcomes). The present study attempts to minimize such confounding by selecting comparison patients that are as similar as possible to BENLYSTA cohort and will also attempt to account for confounding by further adjustment in the analysis using relevant statistical methods (such as propensity score matching or adjustment for baseline factors) (see Section 6.2). However, as with all non-randomized observational studies, residual unmeasured confounding may still exist. In addition, although the study is designed to specifically attempt to enroll a sample of SLE patients who are closely matched in both cohorts, it may be that the final enrolled study sample is not as well matched as desired due to multiple patient factors that can't be controlled for. The Sponsor will monitor enrollment for the proportion of patients who are treatment initiators versus current users and communicate to the sites the interest to achieve a reasonable balance for both groups.

Patients receiving commercially available belimumab may be seen more often by their medical care providers as compared to the bi-annual visits of standard of care patients. This may create

a reporting bias with increased reporting of events for some outcomes in the BENLYSTA group.

11 Study Administration

This study is sponsored by GlaxoSmithKline (GSK) LLC. They will lead on the operational conduct of this observational study world-wide working with contract research organizations.

11.1 Informed Consent

The consent form must be approved by the Institutional Review Board (IRB) or Institutional Ethics Committee (IEC) and contain all elements required by national, state, local, and institutional regulations or requirements. In the event that local regulations/laws require a Privacy Authorization this will be included as part of the informed consent process. Informed consent will be obtained by investigators for each patient whose data are included in this study. A copy of the signed informed consent must be given to each study patient.

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

Regulatory approval or notification will be obtained or performed, respectively, in countries where this is required. IRB/IEC approval will be obtained by participating investigators or a representative thereof; however, application will be made to central IRBs/IECs governing regions or countries wherever this is feasible.

11.3 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 or 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 patients prior to enrollment and must be used to obtain informed consent from patients already enrolled if they are affected by the amendment.

11.4 Data Management

The investigator is responsible for maintaining accurate, complete, and up-to-date records for each patient. 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 patients must be maintained. For data collection and management purposes, patients are to be identified by a patient number only. Documents that identify the patient beyond patient number will not be submitted to the sponsor (eg, the signed informed consent document; patient 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 patient through electronic case report forms (eCRFs) using an Electronic Data Capture (EDC) system provided and approved by the sponsor. Sites must complete the eCRFs in a timely manner and the investigator must promptly review the completed eCRFs for each patient. As the person ultimately responsible for the accuracy of all eCRF data, the investigator must sign the Investigator's Statement in each patient'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 the eCRFs for each of their patients.

11.5 Study Conduct

The study sponsor or designee will monitor the conduct of the study. The sponsor may review eCRFs 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. Monitors or auditors representing the sponsor may also similarly evaluate the study. For these purposes, the investigator will make eCRFs 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 GlaxoSmithKline of any audits they have scheduled with any regulatory authority.

11.6 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.

11.7 Publication Policy

Reports to regulatory authorities will be provided as appropriate and agreed with the relevant authorities.

This study is a multi-center observational research study. Data from all sites participating in the multi-center observational initiative will be pooled and analyzed. The investigators acknowledge that an independent, joint publication is anticipated to be authored by the investigators of the multi-center study and the sponsor's representatives. Neither the participating institutions nor the principal investigators shall publish or present the results of the study prior to the publication of the multi-center study publication. The investigators agree that the sponsor will be the coordinator and arbitrator of all multi-center study publications. For multi-center studies, no investigator will be authorized to publish study results from an individual center until the earlier of the multi-center study results are published or 12 months after the end or termination of the multi-center study 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 the 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.

11.8 Study or Study Site Termination

If the sponsor, 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 the sponsor and the investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- Sufficient information has accumulated to meet the primary scientific objectives of the observational study.
- Other methods of gathering appropriate information become achievable or are deemed preferable.
- The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or losses to follow-up.

The study site may warrant termination under the following conditions:

- Failure of the investigator to enroll patients 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 GSK, study monitor, or the regulatory authority.
- Insufficient adherence to protocol requirements.

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List of Appendices

Appendix 1 Opportunistic Infections and Other Infections of Interest

Opportunistic infections and other infections of interest are a subset of infections that are caused by organisms that usually do not cause disease in immunocompetent individuals but which may cause illness, or more severe illness, when the immune system is suppressed. Since there are no general guidelines for labeling pathogens as opportunistic without considering the host's immune condition, identification of opportunistic infections and other infections of interest in this study is based on the following list of pathogens which when present may indicate immune suppression in a patient. Pathogens considered to cause opportunistic infections and other infections of interest include but are not limited to the following:

Acinetobacter infection

Aspergillosis

Blastomycosis, extrapulmonary

Candidiasis of esophagus, bronchi, trachea, or lungs

Coccidiomycosis, dissemintaed or extrapulmonary

Cryptococcosis, extrapulmonary

Cryptosporidiosis infection, chronic intestinal (> 1 month duration)

Cytomegalovirus disease (other than liver, spleen, or nodes)

Herpes simplex bronchitis, pneumonitis, or esophagitis

Disseminated herpes zoster or involving at least 2 distinct episodes

Herpes virus associated Kaposi's sarcoma

Histoplasmosis disseminated or extrapulmonary

Human polyomavirus infection

Isosporiasis, chronic intestinal (> 1 month’s duration)

Listeriosis

Mycobacterium avium complex or M. Kansasii, disseminated or extrapulmonary

Mycobacterium infections, other species or unidentified species, disseminated or extrapulmonary (eg, M. haemophilium, M. fortuitum, or M. marinum)

Nocardiosis

Polyomavirus (JC virus or BK virus)-associated nephropathy (including progressive multifocal leukoencephalopathy)

Pneumocystis jiroveci infection

Toxoplasmosis of brain

Other infections of interest that should be recorded in this registry, but which are not generally considered opportunistic, include:

Mycobacterium tuberculosis, any site, latent or active

Salmonella sepsis

Hepatitis B

Hepatitis C

All other (ie, non-disseminated or single episode) herpes zoster (shingles)

Appendix 2 Serious Psychiatric Events

The following events suggesting serious mood disorders (including suicidality) and anxiety will be collected if serious.

Adjustment disorder
Adjustment disorder with anxiety
Adjustment disorder with depressed mood
Adjustment disorder with disturbance of conduct
Adjustment disorder with mixed anxiety and depressed mood
Adjustment disorder with mixed disturbance of emotion and conduct
Affective disorder
Agitated depression
Anxiety
Anxiety disorder
Anxiety disorder due to a general medical condition
Bipolar I disorder
Bipolar II disorder
Bipolar disorder
*Completed suicide
Cyclothymic disorder
Depressed mood
Depression
Depression post-operative
*Depression suicidal
Depressive delusion
Depressive symptom
Dysthymic disorder
Generalised anxiety disorder
*Intentional overdose
*Intentional self-injury
Major depression
Menopausal depression
Mood disorder due to a general medical condition
*Multiple drug overdose intentional
*Poisoning deliberate
Postpartum depression
*Self injurious behaviour
*Self-injurious ideation
*Suicidal behaviour
*Suicidal ideation
*Suicide attempt

In order to collect additional information on potential suicidality-related events, should any of the events indicated with the asterisk occur, the investigator will be requested to complete the Possible Suicidality-Related History Questionnaire (PSRHQ, only the first time a serious suicidality-related event is reported) and a Possible Suicidality-Related Questionnaire (PSRQ) (each time a serious suicidality-related event is reported). The PSRHQ collects past medical history in relation to SLE-related neuropsychiatric events prior to study enrollment. The PSRQ collects other information important for evaluating suicidality-related events such as use of illicit drugs, alcohol, other stressors, family history of suicidality and other psychiatric disorders. The PSRHQ and PSRQ are provided in Appendix 3 and Appendix 4, respectively.

Appendix 3 Possible Suicidality-Related History Questionnaire (PSRHQ)

Date of Assessment: _____

(DDMMMYYYY)

Has the subject had any SLE-related neuropsychiatric events prior to study start? ❑Yes ❑No

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

	Event	**Date** (DDMMMYYYY)
❑	Acute Confusional State	
❑	Acute Inflammatory Demyelinating Polyradiculoneuropathy (Guillain-Barré Syndrome)	
❑	Anxiety Disorder	
❑	Aseptic Meningitis	
❑	Autonomic Disorder	
❑	Cerebrovascular Disease	
❑	Cognitive Dysfunction	
❑	Demyelinating Syndrome	
❑	Headache	
❑	Mononeuropathy Single	
❑	Mononeuropathy Multiplex	
❑	Mood Disorders	
❑	Movement Disorder (Chorea)	
❑	Myasthenia Gravis	
❑	Myelopathy	
❑	Neuropathy, Cranial	
❑	Plexopathy	
❑	Polyneuropathy	
❑	Psychosis	
❑	Seizures and Seizure Disorders	

Appendix 4 Possible Suicidality-Related Questionnaire (PSRQ)

Is the subject currently using illicit drugs? ❑ Yes ❑ No

If Yes, check all that apply:
❑ Amphetamines ❑ Benzodiazepines ❑ Cannabinoids ❑ Cocaine ❑ Opiates
❑ Other, Specify: _____

Is the subject currently using alcohol? ❑ Yes ❑ No

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

Has the subject experienced any recent stress? ❑ Yes ❑ No

If Yes, check all that apply:
❑ Family Problems ❑ Relationships ❑ Employment/ Unemployment ❑ Finances
❑ Other Factors, Specify:

Any family history of suicidality? ❑ Yes ❑ 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? ❑ Yes ❑ No

If Yes, specify disorder next to all that apply:

Father _____

Mother _____

Sibling _____

Other _____

Appendix 5 SLICC/ACR Damage Index (SDI)

System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	1
Retinal change or optic atrophy	1
Neuropsychiatric	
Cognitive impairment (eg memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance levels) or major psychosis	1
Seizures requiring therapy for 6 months	1
Cerebrovascular accident ever (score 2 > 1)	1 (2)
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Estimated or measured glomerular filtration rate < 50%	1
Proteinuria > 3.5 gm/24hours	1
Or	
End-stage renal disease (regardless of dialysis or transplantation)	3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	1
Pulmonary fibrosis (physical and radiograph)	1
Shrinking lung (radiograph)	1
Pleural fibrosis (radiograph)	1
Pulmonary infarction (radiograph)	1
Cardiovascular	
Angina or coronary artery bypass	1
Myocardial infarction ever (score 2 if > 1)	1 (2)
Cardiomyopathy (ventricular dysfunction)	1
Valvular disease (diastolic, murmur, or systolic murmur > 3/6)	1
Pericarditis for 6 months, or pericardiectomy	1
Peripheral vascular	
Claudication for 6 months	1
Minor tissue loss (pulp space)	1
Significant tissue loss ever (eg loss of digit or limb)(score 2 if > 1 site)	1 (2)
Venous thrombosis with swelling, ulceration, or venous stasis	1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver, or gall bladder ever, for cause any (score 2 if > 1 site)	1 (2)
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture or upper gastrointestinal tract surgery ever	1

Musculoskeletal	
Muscle atrophy or weakness	1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1
Avascular necrosis (score 2 if > 1)	1 (2)
Osteomyelitis	1
Skin	
Scarring chronic alopecia	1
Extensive scarring or panniculum other than scalp and pulp space	1
Skin ulceration (excluding thrombosis) for > 6 months	1
Premature gonadal failure	1
Diabetes (regardless of treatment)	1
Malignancy (exclude dysplasia) (score 2 if > 1 site)	1 (2)

(From the Systemic Lupus International Collaborating Clinics (SLICC) and the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee, 1996)

Gladman EM, Ginzler E, Goldsmith C et al. SLICC/ACR damage index for SLE. Arthritis Rheum 1996a;39(3):363-9.

Appendix 6 SLEDAI 2000

Score if descriptor is present at time of visit or ± 30 days of enrollment visit.

Weight	SLEDAI Score	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Excluded uremia and drug causes.
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory or other intelligent function, with rapid onset fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serious exodate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual, infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e. tenderness, swelling, or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/adolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	> 5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	> 0.5 gm/24 hours.
4	_____	Pyuria	> 5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	> 38°C. Exclude infectious cause.
1	_____	Thrombocytopenia	< 100,000 platelets/ $x10^9$/L, exclude drug causes.
1	_____	Lenkopenia	< 3,000 White blood cell/ $x10^9$/L, exclude drug causes.
TOTAL SLEDAI SCORE	_____		

Adapted from:

Dafna D Gladman, Dominique Ibañez and Murray B Urowitz, Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29;288-291.

Appendix 7 Potential Confounders for Malignancies and/or Infections List

- **Demographic and other general characteristics**
  - Age
  - Gender
  - Weight
  - Height
  - Race/ethnicity
  - Smoking history
  - Family history of cancer – first degree relatives & grandparents
  - Alcohol history
  - Female only:
  - Parity
  - Hormonal status

- **SLE disease profile**
  - Age at diagnosis
  - Organ involvement (SLEDAI 2000 Domains)
  - Disease Severity (SLEDAI 2000)
  - Organ Damage (SDI)
  - ANA status
  - Anti-dsDNA status
  - Quantitative Immunoglobulins (IgG, IgA, IgM)
  - Complement levels (C3/C4)
  - Total white blood cell count
  - Neutrophil differential %
  - Lymphocyte differential %

- **SLE treatment**
  - Name and duration of current SLE medications: including anti-malarials, biologics, steroids, and immunosuppressants at baseline
  - In addition, for steroids add dose

- **Co-morbidities**
  - ESRD/dialysis
  - Hepatitis B
  - Hepatitis C
  - HIV
  - Sjogren's Syndrome (Secondary)
  - Neutropenia
  - Post-transplant (any transplant)
  - Diabetes
  - Splenectomy

- Chronic lung disease
- Known immunoglobulin deficiencies
- Tuberculosis (latent or active)
- History of cancer (including NMSC)
- History of serious infection

- **Vaccinations**
  - BCG
  - Pneumococcal
  - Influenza vaccine
  - Human papillomavirus (HPV)
  - Hepatitis
  - Varicella zoster
  - Any live vaccine received 30 days prior to enrollment

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Reason for signing: Approved	[redacted]

Reason for signing: Approved	[redacted]

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