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PPD

Revision Chronology

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2010N108011_00	2011-JUL-21	Original
2010N108011_01	2012-FEB-24	Amendment No. 01 Global: Update HGS Sponsor Signatory information Update Abbreviations Update Protocol Summary Update Methodology (Section 4) Update Summary Table of Evaluations, including addition of breastfeeding status Update Reporting of Adverse Events (Section 7.4) Update References Update Appendices Minor typographical errors corrected
2010N108011_02	2013-APR-11	Amendment No.02: Global Registry name change to use generic in title vs. brand name Update Sponsor Signatory Page Delete HGS Sponsor Signatory Page Delete HGS Sponsor Contact Information Delete HGS Protocol Number Delete HGS Study Number Update Investigator Protocol Agreement Page Removal of HGS throughout body of protocol Update Trademark Information Update Protocol Summary Revise definition for retrospective reports of pregnancy; addition of definitions for traditional prospective and pure prospective reports of pregnancy per the

		EMA in the following sections: • Protocol Summary • Update Section 4.1 • Update Section 4.2 • Update Section 4.6 • Update Section 4.8 • Update Section 5 • Update Section 6 • Update Glossary Update Section 4.5 Update Section 7.2 Update Section 7.4 Update Section 7.7 Update Section 7.9 Update References Update Appendices Minor typographical errors corrected
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		• Update Section 4.6.3.1 • Update Section 4.6.3.2 • Update Section 4.6.4 • Update Section 4.6.8.4 • Update Section 4.8 • Update Section 4.8.1 • Update Section 4.8.2 • Update Section 4.8.2.1 • Update Section 4.8.2.2 • Update Section 4.8.3 • Update Section 4.8.4 • Update section 4.8.5 • Update Section 6 • Update Section 7.4 • Update Section 7.10 • Update Section 7.11 • Update Section 7.12 Update Section 3 Update Section 4.3.1 Update Table of Evaluations (Section 4.6.1) Update Section 4.6.3 Update Section 4.6.4 Update Section 4.6.8.1 Update Section 4.6.8.2 Update Section 7.13 Update References Update Appendices Update Glossary Minor typographical errors corrected
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		required due to sponsor site closure Updates to Section 4.6.8.3 Updates to Section 7.4 Minor typographical/editorial errors corrected

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number: 2010N108011_04

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

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

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

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

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
aCL	anti-cardiolipin antibodies
ACOG	American Congress of Obstetricians and Gynecologists
AE	Adverse Event
BCMA	B cell maturation antigen
BLyS	B lymphocyte stimulator
BR3	BLyS receptor 3
CDC	Centers for Disease Control and Prevention
CEDD	corrected estimated date of delivery
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CSD	Central safety department
EC	Ethics Committee
EDD	estimated date of delivery
EMA	European Medicines Agency
EUROCAT	European Surveillance of Congenital Anomalies
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
HCP	health care provider
HGS	Human Genome Sciences
HIPAA	Health Insurance Portability and Accountability Act
ICMJE	International Committee of Medical Journal Editors
IB	investigator's brochure
IRB	Institutional Review Board
IV	Intravenous
LMP	last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MSL	medical science liaison
PBRER	Periodic benefit risk evaluation report
PGA	Physician Global Assessment
RAP	Reporting and Analysis Plan
SABLE	Safety and Effectiveness of Belimumab in Systemic Lupus Erythematosus
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SDI	SLICC/ACR Damage Index
SELENA	Safety of Estrogen in Lupus Erythematosus National Assessment
SGA	small for gestational age
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index

SLE	systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
TACI	transmembrane activator–1 and calcium modulator and cyclophilin ligand–interactor
TNF	tumor necrosis factor
US	United States
USA	United States of America
WHO	World Health Organisation

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PROTOCOL SUMMARY

Protocol No.:	BEL114256
Protocol Title:	Belimumab (BENLYSTA) Pregnancy Registry Protocol
Products:	Belimumab
Clinical Phase:	Phase IV: Observational Pregnancy Drug Exposure Registry
Study Center:	Each country participating in the registry will have a central registry site and principal investigator. The Registry Coordinating Center will be responsible for the overall daily management of the registry and will facilitate all data collection and management activities.
Objective:	The main objective is to evaluate pregnancy and infant outcomes for pregnancies in women with SLE exposed to commercially supplied belimumab within the 4 months prior to and/or during pregnancy. In addition, pregnancy and infant outcomes will also be collected for pregnancies in women with SLE from the SABLE (Safety and Effectiveness of Belimumab in Systemic Lupus Erythematosus) protocol who are not exposed to belimumab.
Endpoints:	<u>The primary endpoint is</u>: • Birth defects <u>Secondary endpoints include</u>: • *Other pregnancy outcomes* • Spontaneous miscarriage • Live birth (including preterm birth and small for gestational age) • Stillbirth • Elective termination *Infant outcomes through age 1 year* • Serious and/or clinically significant infections
Study Design:	This global pregnancy registry will be a multi-center, prospective cohort study with voluntary participant registration following informed consent. The registry will be strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating health care provider (HCP). The registry will collect data that are

	routinely documented in the participant's medical record in the course of usual clinical care.
Study Procedures:	Data will be collected at registration, at the end of the second trimester (approximately 26 weeks' gestation), and at pregnancy outcome (delivery or early termination). For live births, infant data will be collected at pregnancy outcome and at 4 and 12 months of age. The registry will perform targeted follow-up to collect additional data on events and outcomes of interest.
Study Population	Minimum criteria for enrolment will be the following: • Exposure criteria: • <u>For belimumab exposed pregnant women;</u> Sufficient evidence to confirm that exposure to commercially supplied belimumab occurred within the 4 months prior to and / or during pregnancy ("belimumab exposed") Or • <u>For belimumab unexposed pregnant women:</u> Any women who became pregnant during the SABLE protocol and was not exposed to belimumab: Sufficient evidence to confirm that exposure to belimumab did not occur within 4 months prior to and / or during pregnancy ("unexposed") • Sufficient information to classify the pregnancy report as prospective or retrospective. Retrospective reports of pregnancy are those in which the pregnancy ended before enrollment or at the time of first contact with the registry. Two definitions for prospective reports of pregnancy will be used in this registry, traditional prospective and pure prospective: Traditional prospective reports of pregnancy will include all women who enroll in the registry before the end of pregnancy (live birth, fetal loss, etc), regardless of known normal or abnormal prenatal test results Pure prospective reports of pregnancy are a subset of traditional prospective reports and include those where (a) the enrollee did not know at the time of enrollment whether the fetus had a malformation, and (b) no prenatal testing was completed prior to enrollment. • Full initial reporter (i.e., pregnant woman or HCP)

	contact information to allow for follow-up (name, address, telephone number/email address) and contact information for applicable HCPs if the initial reporter is the pregnant woman. • Consent provided by the pregnant woman for her participation and assent for participation of her infant. This registry is intended to enroll participants with SLE. If a pregnancy is reported into the registry in a woman who is not diagnosed with SLE, the registry will collect that data. However, outcomes in participants not having SLE or their offspring will be summarized separately from outcomes in participants having SLE or their offspring.
Comparison Data:	The registry includes unexposed participants from the SABLE protocol, however, as the likely number of these participants will be small, formal comparisons of primary and secondary outcomes between belimumab exposed and unexposed participants will not be conducted. Data obtained may be compared with external data sources including information obtained from the literature, birth defects surveillance systems (e.g., Centers for Disease Control and Prevention [CDC] Metropolitan Atlanta Congenital Defects Program [MACDP], European Surveillance of Congenital Anomalies [EUROCAT]), and external SLE cohorts and/or autoimmunity cohorts as data are available and appropriate.
Number of Participants:	The registry will seek to enroll approximately 500 traditional prospective pregnancies exposed to commercially supplied belimumab. Research indicates that approximately 83-95% of pregnancies enrolled in pregnancy exposure registries will result in a live birth; of these, approximately 20-25% will be lost to follow-up, resulting in an upper estimate of 380 live births and a lower estimate of 311 live births. Furthermore, the registry will enroll as many unexposed participants as possible from the SABLE protocol.

Statistical/Analytical Methods:	Descriptive statistics will be calculated separately for traditional prospective and for pure prospective evaluable data for belimumab-exposed subjects. The summary statistics for continuous and categorical variables to be used will be specified in the Reporting and Analysis Plan (RAP) but may include means, standard deviations, medians, minimums, maximums, percentiles, and percentages. Frequencies and proportions of adverse pregnancy outcomes, birth defects, serious and/or clinically significant infections in infants will be calculated with corresponding 95% confidence intervals for both the exposed and unexposed groups. For the primary endpoint of birth defect prevalence, the estimates of birth defect prevalence from MACDP and EUROCAT will be used to represent external population comparators. The differences between the observed registry birth defect rates and these comparators will be estimated along with 95% confidence intervals.

1. INTRODUCTION

1.1. Background

Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect a wide range of organ systems, mainly the skin and musculoskeletal system but also the kidney, heart, lungs, and central nervous system. A total of 11 American College of Rheumatology (ACR) criteria have been established for disease classification, with a minimum of 4 criteria indicating SLE disease [Petri, 2005].

In the United States (US), the estimated average of the reported prevalences of SLE is approximately 10 cases per 10,000 persons, representing about 300,000 patients, and the incidence increased 2.5-fold between 1950 and 1979 [Uramoto, 1999; Somers, 2007, Balluz, 2001; Naleway, 2005; Ward, 2004; Helmick, 2008]. In the European Union, an estimated overall average of the reported prevalences is 4 to 5 cases per 10,000 persons [Alamanos, 2003; Benucci, 2005; Eilertsen, 2006; Gourley, 1997; Govoni, 2006; Gudmundsson, 1990; Hopkinson, 1993; Johnson, 1995; López, 2003; Nightingale, 2007; Nossent, 2001; Piette, 2004; Samanta, 1992; Ståhl-Hallengren, 2000; Voss, 1998]. As many as 4 million people may be affected worldwide.

More patients with lupus are women than men; the female-to-male ratio in the childbearing years has been reported to be as high as 12:1 [Danchenko, 2006]. In women, SLE typically develops between ages 15 and 44 years, and onset is most likely insidious [Danchenko, 2006]. Complications during pregnancy can include lupus flares, worsening or new onset of renal failure, hypertension, preeclampsia, pulmonary embolism, deep vein thrombosis, major infections, bleeding and thrombotic events. Of the 63 women in the Lupus in Minorities; Nature vs. Nurture (LUMINA) cohort who became pregnant during follow-up, 76% developed complications [Andrade, 2006]. Pregnancy remains contraindicated in SLE patients with severe pulmonary hypertension or restrictive lung disease, heart failure, chronic renal failure, previous severe preeclampsia, HELLP (hemolysis, elevated liver enzyme levels and a low platelet count) despite therapy with aspirin and heparin, and in SLE patients with stroke or severe lupus flare within the previous 6 months [Ruiz-Irastorza, 2011].

Complications of lupus pregnancy can be minimized with careful screening and close cooperation across the health care team. Careful attention to the impact of concomitant medications has had a positive impact on the outcome of pregnancies [Ruiz-Irastorza, 2009; Ruiz-Irastorza, 2011].

In addition to challenges to maternal health, patients with lupus have poor obstetric outcomes compared with women without SLE, including a greater likelihood of fetal loss (approximately 3-fold increase) and a greater incidence of preterm deliveries [~40% vs. 10% among healthy women] [Clark, 2003; Clowse, 2005]. Recently a meta-analysis addressing this subject was reported [Smyth, 2010]. The proportion of pregnancies in women with SLE resulting in fetal death has been reported to be 15-20% in European studies [Cortes-Hernandez, 2002; Julkunen, 1993] and 15-25% in North American studies [Clowse, 2005; Andrade, 2008], with stillbirths accounting for 2-4% of these outcomes.

The presence of anti-phospholipid antibodies has been reported in 30-80% of patients with SLE [Mecacci, 2009], and associated with an increased risk of spontaneous miscarriage and poor maternal and/or fetal outcome [Cortes-Hernandez, 2002, Clark 2007]. In prospectively examined pregnancies, with anti-Ro and anti-La antibodies in the mother, the prevalence of congenital heart block (with mortality of approximately 20-30%) is between 1 and 5%, and rises to between 6 and 25% when another pregnancy was affected in the same mother [Jaeggi, 2010; Friedman, 2010]. Active SLE and associated comorbidities (proteinuria, anti-phospholipid syndrome, thrombocytopenia, and hypertension) have also been noted to be important predictors of fetal loss [Clowse, 2006; Cortes-Hernandez, 2002; Julkunen, 1993].

A cohort of SLE pregnancies from a single academic medical center in the US identified risk factors for fetal loss and preterm delivery. Among pregnant patients with high SLE disease activity (PGA score ≥2), 42% had fetal loss during the first trimester compared to 14% among women with low activity (PGA<2). This pattern was observed during the second (32% vs.7%, respectively) and third trimesters (10% vs. <1%, respectively). The combination of high disease activity, with low complement and/or anti-ds DNA autoantibodies, during the second trimester increased the risk of fetal loss and preterm delivery pregnancy outcomes [Clowse, 2011].

B-lymphocyte stimulator (BLyS), a 285-amino acid protein and member of the tumor necrosis factor (TNF) ligand superfamily, is a B cell survival factor that inhibits apoptosis and stimulates the differentiation of B cells into immunoglobulin-producing plasma cells [Moore, 1999; Do, 2000]. In humans, soluble BLyS is biologically active and produced primarily by monocytes and activated neutrophils [Moore, 1999; Scapin, 2008]. BLyS can bind to 3 receptors on B lymphocytes: BLyS receptor 3 (BR3; also known as BAFF-R), transmembrane activator–1 and calcium modulator and cyclophilin ligand–interactor (TACI), and B cell maturation antigen (BCMA) [Cancro, 2004; Gross, 2000; Xia, 2000; Yan, 2000]. BLyS is over expressed in patients with SLE and other autoimmune diseases, and BLyS levels correlate with disease activity [Cheema, 2001; Zhang, 2001; Groom, 2002; Mariette, 2003; Petri, 2008; Daridon, 2009]. Belimumab is a recombinant, human, IgG1λ monoclonal antibody that binds soluble BLyS with high affinity and inhibits its biological activity [Baker, 2003]. Following in vitro and animal model studies [Belimumab Investigator's Brochure [IB], 2010], belimumab was identified as a potential therapeutic agent for autoimmune diseases in which BLyS may play a role in disease pathogenesis.

No data are available from human subjects who received substantial exposure to belimumab during pregnancy, as women who became pregnant in belimumab clinical trials were withdrawn from treatment as soon as the pregnancy was detected through monthly pregnancy screening. However, in a study of prenatal and postnatal development conducted in cynomolgus monkeys, pregnant monkeys received belimumab by IV injection at approximately gestation day 20-22 and every 2 weeks thereafter until parturition [Belimumab IB, 2010]. Treatment with belimumab was not associated with direct or indirect harmful effects with respect to maternal toxicity, developmental toxicity, or teratogenicity. Treatment-related findings were limited to expected reduction of B cells and IgM in both dams and infants. B-cell numbers recovered after the cessation of belimumab treatment by about 1 year post-partum in adult monkeys and by 3

months of life in infant monkeys. IgM levels in infants exposed to belimumab in utero recovered by 6 months of age. Study data revealed the passage of belimumab across the placenta and excretion of belimumab into the milk of nursing female monkeys.

Human Genome Sciences Inc. (HGS) and GlaxoSmithKline (GSK) have completed Phase 3 studies for the use of belimumab in SLE. In the Phase 3 studies (HGS1006-C1056, N=865 and HGS1006-C1057, N=819) autoantibody-positive patients with active SLE were administered either intravenous (IV) belimumab (1 or 10 mg/kg) or placebo in addition to their baseline medications for lupus. Active disease was considered to be a Safety of Estrogen in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) ≥6. In the Phase 3 studies, 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. Evidence of benefit in other clinical measures such as reductions in disease activity as measured by SELENA-SLEDAI, severe flare, and reduced steroid use were also observed.

The primary safety population supporting approval of belimumab also included data from a Phase 2 study in 449 subjects with SLE (LBSL02). 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. 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%; as with other immunomodulating agents, the mechanism of action of belimumab might be expected to increase the risk for the development of malignancies. Hypersensitivity and infusion reactions were observed. 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.

Within the IV SLE studies, the number of pregnancies was small; 60 pregnancies (belimumab: 54; placebo: 6) with 50 known outcomes (belimumab: 44; placebo: 6) had been reported as of 31 December 2010. Subjects had been instructed to use contraception, had pregnancy tests before each belimumab or placebo infusion, and were withdrawn from treatment if the test was positive. Regardless of treatment, the incidence of fetal loss in the IV SLE studies was greater than the expected 15-25% fetal loss reported in the literature [Andrade, 2008; Clowse, 2005; Rahman, 1998; Yasmeen, 2001]. In subjects with known pregnancy outcomes (excluding elective terminations), fetal loss was reported for 13/34 pregnancies among subjects exposed to

belimumab and in 3/3 subjects exposed to placebo. When aCL status (including IgG, IgM and / or IgA aCL positivity) was examined in the pregnancies that resulted in fetal loss; 7/13 subjects who received belimumab and 2/3 subjects who received placebo were aCL positive. In the 21 patients receiving belimumab with live birth pregnancy outcomes, 4/21 subjects were aCL positive. The interpretation of these data is limited by the very small number of pregnancies.

1.2. Rationale

This global Belimumab Pregnancy Registry will collect prospective data on pregnancies and pregnancy outcomes on a voluntary basis in women with SLE who have received commercially supplied belimumab within the 4 months prior to and/or during pregnancy ("exposed" patients) and in those women with SLE that have not received belimumab within the 4 months prior to and/or during pregnancy ("unexposed" patients) from the Safety and Effectiveness of Belimumab in Systemic Lupus Erythematosus (SABLE) protocol. The unexposed patient group was added to this registry at the request of the European Medicines Agency (EMA).

The registry will also evaluate outcomes of infants born to both exposed and unexposed mothers. This registry will add to the current clinical experience with belimumab and will complement reproductive data from animal toxicology studies. It will also assist clinicians in weighing the potential risks against the benefits of treatment for individual patients with SLE.

GSK will sponsor the Belimumab Pregnancy Registry in countries where it holds Marketing Authorization and where belimumab is available by prescription.

2. OBJECTIVE AND ENDPOINT (S)

2.1. Objective

The main objective is to evaluate pregnancy and infant outcomes for pregnancies in women with SLE exposed to commercially supplied belimumab within the 4 months prior to and/or during pregnancy.

In addition, pregnancy and infant outcomes for pregnancies in women with SLE from the SABLE (Safety and Effectiveness of Belimumab in Systemic Lupus Erythematosus) protocol who are not exposed to belimumab will also be evaluated.

2.2. Endpoints

Primary Endpoint:

- Birth defects

Secondary Endpoints:

Other pregnancy outcomes

- Spontaneous miscarriage

- Live birth (preterm birth and small for gestational age (SGA))
- Stillbirth
- Elective termination

Infant outcomes through age 1 year

- Serious and/or clinically significant infections

These endpoints are defined in Section 4.3 of the protocol.

3. TARGET AUDIENCE

The ultimate utility of registry data will be to provide clinicians and regulatory agencies with relevant human data on the potential risks and benefits of belimumab exposure so they can more effectively counsel women who have been prescribed belimumab and are pregnant or planning to become pregnant.

Registry interim data reports will be produced at least annually, and a final data report will be produced at the conclusion of the registry. Interim and final reports will be made available to HCPs and the final report will be submitted to regulatory authorities. Data may also be reported at scientific conferences or published in scientific journals. In addition, GSK central safety department (CSD) will produce periodic benefit risk evaluation reports (PBRER) for submission to regulatory authorities.

4. METHODOLOGY

4.1. Study Population

Minimum criteria for enrollment will be the following:

- Exposure classification:
  - For belimumab exposed pregnant women:

    Sufficient evidence to confirm that exposure to commercially supplied belimumab occurred within the 4 months prior to and/or during pregnancy ("belimumab exposed")

    Or
  - For belimumab unexposed pregnant women:

    Sufficient evidence to confirm that exposure to belimumab did not occur within 4 months prior to and / or during pregnancy ("unexposed")
- Sufficient information to classify the pregnancy report as prospective or retrospective (Section 4.6.8.1 and Section 4.6.8.2). Retrospective reports of pregnancy are those in which the pregnancy ended before enrollment or at the time of first contact with the registry. Two definitions for prospective reports of pregnancy will be used in this registry, traditional prospective and pure prospective:

Traditional prospective reports of pregnancy will include all women who enroll in the registry before the end of pregnancy (live birth, fetal loss, etc), regardless of known normal or abnormal prenatal test results

Pure prospective reports of pregnancy are a subset of traditional prospective reports and include those where (a) the enrollee did not know at the time of enrollment whether the fetus had a malformation, and (b) no prenatal testing was completed prior to enrollment.

- Full initial reporter (i.e., pregnant woman or HCP) contact information to allow for follow-up (name, address, telephone number/email address) and contact information for applicable HCPs if initial reporter is the pregnant woman
- Consent provided by the pregnant woman for her participation and assent for participation of her infant

Reported cases that do not meet the minimum criteria for registry enrollment will be ineligible for inclusion in the registry and will not be entered into the database. In such cases, the report will be forwarded to GSK and handled using routine pharmacovigilance measures.

4.2. Study Design

This global pregnancy registry will be a multi-center, prospective cohort study with voluntary participant registration following informed consent by the pregnant woman for her participation and assent for participation of her infant. The registry will be strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating HCP. The registry will collect data that are routinely documented in the participant's medical record in the course of usual care, with the possible exception of the Physician Global Assessment (PGA) of SLE disease activity (Appendix 1) and the SLICC/ACR Damage Index (SDI; Appendix 2). The PGA is a simple, concise, global index of disease activity [Petri, 1992] that will be completed at registration (including a pre-conception assessment), towards the end of 2nd trimester and at pregnancy outcome for registry participants with SLE. SLE disease activity is often assessed in usual clinical care and collection of this information will be integral to evaluating disease severity during the pre-conception period through the end of pregnancy. The SDI records irreversible organ system damage occurring in participants with SLE regardless of etiology. Damage may be attributed to active SLE disease, concomitant medication or intercurrent illness [Gladman, 1996].

Data will be collected at registration (early in pregnancy to include pre-conception SLE disease severity), at the end of the second trimester (approximately 26 weeks' gestation), and at pregnancy outcome (delivery or early termination). For live births, infant outcomes at the time of birth will be reported. Infants will be followed up for outcomes at 4 and 12 months of age. Targeted follow-up will also take place to gather additional information, if required to assist data interpretation on events and outcomes of interest. This registry is intended to enroll participants with SLE.

Retrospective reports of pregnancy are those in which the pregnancy ended (live birth, fetal loss, etc) before enrollment or at the time of first contact with the registry. All

retrospective cases reported to the registry will have data collected and entered into the database (as appropriate for the underlying disease) using the same procedures as prospective cases (traditional or pure); however, retrospective cases will be summarized separately. If a pregnancy is reported to the registry from a woman who is not diagnosed with SLE, the registry will collect that data, but will summarize it separately from the SLE pregnancies (see Section 4.6.8.6).

4.3. Outcome Definitions

4.3.1. Pregnancy Outcomes of Interest

The following pregnancy outcomes will be collected by the registry:

- Spontaneous miscarriage: fetal death or expulsion of products of conception prior to 20 weeks' (<20 weeks) gestation
- Live birth: the birth of a living fetus at 20 weeks' gestation or greater (≥20 weeks), or, if gestational age is unknown, a fetus weighing 500 g or more (≥500 g)
- Stillbirth: a fetal death occurring at 20 weeks' gestation or greater (≥20 weeks), or, if gestational age is unknown, a fetus weighing 500 g or more (≥500 g)
- Elective termination: voluntary interruption of pregnancy, including pregnancy termination that occurs electively, to preserve maternal health, or due to fetal abnormalities
- Preterm birth: an infant born at gestational age less than 37 weeks (<37 weeks)
- Neonatal death: an infant who after live birth expired within the first 28 days (≤28 days) of life
- Ectopic pregnancy: implantation of a conception outside of the uterus
- Molar pregnancy: a conception that results in a gestational trophoblastic tumor
- Small for gestational age (SGA): defined as an infant whose birth weight is less than the 10^{th} percentile for the gestational age. It is based on data derived from an appropriate reference population. The registry will utilize the sex specific international growth reference standards from the International Fetal and Newborn Growth Consortium for the 21^{st} Century (INTERGROWTH-21^{st}) for those born at ≥33 weeks gestational age (Villar, 2014). The INTERGROWTH-21^{st} standards are the latest available global reference standards, representing contemporary information from an international, multiethnic, diverse population and have been specifically developed for modern research. As the INTERGROWTH-21^{st} standards are valid for infants born between $33^{0/7}$ and $42^{6/7}$ weeks gestation, SGA will be additionally classified using the reference standard endorsed by the American Congress of Obstetricians and Gynecologists (ACOG) which is applicable for the entire range of gestational age (Alexander, 1996).

4.3.2. Birth Defects

The registry will define and code birth defects with criteria specified by Centers for Disease Control and Prevention (CDC)'s Metropolitan Atlanta Congenital Defects Program (MACDP) (Birth Defects and Genetic Diseases Branch 6 – Digit Code for Reportable Congenital Anomalies, Version 08/07). Newborn and infant conditions that are not necessarily considered birth defects appear in the Exclusion List for the MACDP. These conditions may be included under certain circumstances by CDC criteria and will be considered "conditional defects" in the registry.

The registry will define a defect as any major structural or chromosomal defect or combination of 2 or more of the conditional defects in live-born infants, stillbirths, or fetal losses of any gestational age (including outcomes prior to 20 weeks' gestation or weighing <500 g). This definition is consistent with, but not restricted to, the CDC MACDP definition. Clusters of conditional defects (as defined by CDC MACDP) and data from aborted fetuses of less than 20 weeks' gestation, when available, will be included to increase sensitivity of monitoring. The MACDP includes conditional defects only if in the presence of a major structural defect. In contrast, this registry will consider reports of 2 or more conditional defects as a birth defect case, to increase potential signal generation and to capture instances where a combination of conditional defects might constitute a major birth defect or syndrome.

The registry will conform to the CDC MACDP guidelines in disqualifying birth defects if those findings are present in infants born at less than 36 weeks of gestation and are attributable to prematurity itself, such as patent ductus arteriosus, patent foramen ovale, or inguinal hernias. The CDC MACDP classification includes chromosomal defects. Though these defects are not likely to contribute to a risk for a drug exposure, the registry will include these birth defects to maintain this consistency with the CDC MACDP.

Live-born infants with only transient or infectious conditions or with biochemical abnormalities (e.g., jaundice) will be classified as being without reported birth defects unless there is a possibility that the condition reflects an unrecognized birth defect. Detected and reported transient or infectious conditions or biochemical abnormalities in infants without reported birth defects and defects that are excluded by the CDC guidelines will be reviewed and noted in an appendix in the registry reports.

Because this registry will be conducted in North America and Europe at a minimum, the registry will use the European Surveillance of Congenital Anomalies (EUROCAT) in addition to the US-based CDC MACDP in subgroup-analyses and/or with specific SLE comparator cohorts, if data are available or applicable.

4.3.3. Serious and/or Clinically Significant Infections in Infants

All infections that meet the serious adverse event criteria as per Section 7.4 will be reported for infants through 12 months of age. Certain non-serious events will additionally be reported as clinically significant and will include:

- Infants from birth through 6 months of age: infections requiring treatment

- Infants from birth through 3 months of age: fevers of unknown origin or of known infectious etiology

4.4. Exposure Definition

For belimumab-exposed subjects: One complete or partial dose of commercially supplied belimumab, administered within the 4 months (i.e., a period of approximately 5 belimumab terminal half-lives) prior to and /or during pregnancy, will constitute exposure. Belimumab exposure will be further categorized by earliest trimester of exposure, as described in Section 4.8.2.2.

For belimumab "unexposed" subjects: Treatment with any immunosuppressants (azathioprine, methotrexate, cyclophosphamide, mycophenolate, biologics or others) as defined in the SABLE protocol as SLE treatment, excluding belimumab (Protocol HGS1006-C1124). There must be sufficient evidence to confirm that exposure to belimumab did not occur within 4 months prior to and / or during pregnancy for a woman to be classified within this group.

4.5. Adverse Drug Experiences / Event Measures

The following outcomes for the registry objectives represent a number of potential adverse drug experiences or events, which include but may not be limited to:

- Reports of congenital anomalies in the fetus or infant
- Reports of adverse pregnancy outcomes, including spontaneous miscarriages and stillbirths
- Reports of serious and/or other clinically significant infections in the infant
- Reports of serious adverse events in the mother or infant

The registry will collect and process all reported serious adverse drug experiences/events as outlined in Section 7.4.

4.6. Data Collection and Management

This is a voluntary registry and the registry awareness program will encourage enrollment as early in pregnancy as possible, so as to minimize bias. In addition, all investigators from the SABLE protocol will be made aware of the Registry and will inform eligible women of their option to co-participate in this Registry. The participants will be followed for the duration of their pregnancies and after birth to ascertain pregnancy and infant outcomes.

The pregnant woman and appropriate members of her health care team will serve as data reporters to the registry. Data regarding participants' SLE disease severity will be sought from the belimumab prescriber to encompass 4 different timepoints (pre-conception, registration, end of second trimester and pregnancy outcome). Data regarding the pregnancy and pregnancy outcome will be sought from the obstetric HCP, and data on live-born infants will be sought from the pediatric HCP. Appropriate members of the woman's and infant's health care team will be contacted to complete missing data as

needed. Participant-reported data will be verified from the HCP overseeing that component of the participant's care. All data will be collected from the participant or the relevant HCP on case report forms (CRF). Medical records will not be requested by the registry unless considered appropriate during targeted follow-up of specific events and outcomes (see Section 4.6.5).

As noted in the following table (Table 1), contact will be made with HCPs at several different time points. Contact with the providers will be timed to maintain interest in the data collection and to minimize loss to follow up. CRF data collection will allow entry of data regardless of when it is obtained and will be associated with gestational age, not with date entered in the CRF. Much of the data collected will be recorded on running logs to facilitate complete data capture.

- Depending on the gestational age at time of enrollment and pregnancy outcome, not all CRFs may be completed for each participant. For example, if a participant enrolls late in pregnancy and delivers early, there may be no second trimester data collection form completed. Additional contacts may occur at the discretion of registry personnel or HCP to complete data collection. At each contact, data from every visit to the HCP since the prior contact between the HCP and the registry will be reviewed for relevance to the registry.
- Belimumab exposures, other SLE treatment, other medications and concurrent medical conditions will be recorded on running logs by the prescriber and obstetric HCPs at each registry contact to capture all relevant data for the pregnancy.
- The data, which are being collected by registry staff, are all clinical data that are routinely documented in medical records during the course of the pregnancy, and may be extracted by the HCPs, thereby minimizing recall bias. All data entered into the registry database will be associated with the gestational age at which the assessment occurred.
- Every clinical event or abnormal value that has been identified will be collected by registry staff regardless of the number of visits the patient makes to any given HCP. All of these data will be associated with the gestational age at which the assessment was made.

To ensure maximum collection of data, the registry will accept data from clinicians at any time from the day a participant is enrolled in the registry through the day that the registry is closed. No date for cessation of data entry into the pregnancy registry on any specific participant will be specified.

The registry will be strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating HCP. There will not be mandatory laboratory tests or assessments required as part of this registry. Only data acquired during the course of routine medical care will be collected, with the possible exception of the PGA of SLE disease activity (Appendix 1) and the SDI (Appendix 2). The PGA is a simple, concise, global index of disease activity that will be completed at registration (including a pre-conception assessment), towards the end of 2nd trimester and at pregnancy outcome for registry participants with SLE. SLE disease activity is often assessed in usual clinical care and collection of this information will be integral to

evaluating disease severity during the pre-conception period through the end of pregnancy. Every effort will be made to collect PGA data for the 6 month period prior to conception, at registration and towards the end of 2nd trimester. In addition, PGA will be collected at pregnancy outcome to reflect disease activity for the entire pregnancy. The SDI records irreversible organ system damage occurring in participants with SLE regardless of etiology. Damage may be attributed to active SLE disease, concomitant medication or intercurrent illness [Gladman, 1996].

Study procedures and enrollment criteria will be consistent among all participants per local laws and regulations.

4.6.1. Summary Table of Evaluations

Table 1 Table of evaluations

Information Requested	Data Source[a]	Registration	Interim Prenatal Follow-up (end of 2nd trimester)	Pregnancy Outcome	Infant Follow-up (4 & 12 months)	Targeted Follow-up
Maternal Information						
Maternal contact information, alternate contact information, HCP contact information	Participant and/or HCP	✓	✓[b]	✓[b]	✓[b]	
Maternal characteristics (age, ethnicity, etc)	Obstetric HCP	✓				
Maternal prenatal information (LMP, EDD, CEDD, prenatal imaging and aneuploidy screening/testing results & timing)	Obstetric HCP	✓	✓[b]	✓[b]		
Maternal disease severity (to include pre-conception assessment)[c]	SLE treatment Prescriber	✓	✓[b]	✓[b]		
Obstetrical history	Obstetric HCP	✓	✓[b]			✓[d]
Family history of birth defects	Obstetric HCP					✓[d]
Belimumab or other SLE treatment exposure information	SLE treatment Prescriber	✓	✓[b]	✓[b]	✓	✓[b]
Concurrent conditions, concomitant medications, pregnancy complications, alcohol, tobacco and recreational drug use during pregnancy	SLE treatment Prescriber and/or Obstetric HCP	✓	✓[b]	✓[b]		

Information Requested	Data Source[a]	Registration	Interim Prenatal Follow-up (end of 2nd trimester)	Pregnancy Outcome	Infant Follow-up (4 & 12 months)	Targeted Follow-up
Pregnancy Outcome Information						
Pregnancy status	Obstetric HCP	✓	✓	✓[b]		
Outcome information (live birth, fetal loss, weight)	Obstetric HCP	✓[e]	✓[e]	✓		
Birth defect noted & description	Obstetric HCP	✓[e]	✓[e]	✓		
Contributing factors	Obstetric HCP	✓[e]	✓[e]	✓		✓[d]
Infant Follow-up Information						
Birth defect noted & description	Pediatric HCP			✓	✓[f]	✓[d]
Contributing factors	Pediatric HCP			✓	✓[f]	✓[d]
Developmental milestones	Pediatric HCP				✓[f]	
History of serious and/or clinically significant infections, fevers of unknown origin, treatment, & outcomes	Obstetric and/or Pediatric HCP			✓[f]	✓[f]	✓[d]
Breastfeeding status	Obstetric and/or Pediatric HCP			✓	✓[f]	

a. Under ideal circumstances, the registry will collect data from the data source noted. Should there be extenuating circumstances that preclude data collection from the identified source; the registry may seek the data from a secondary source. Every effort will be made to verify patient reported data.
b. Obtain updated information since the previous contact.
c. Includes maternal disease severity pre-conception and at registration. If a registry participant does not have SLE, SLE specific assessments will not be required.
d. Collect information not previously obtained, to facilitate characterization of the fetal loss, birth defects or serious and/or clinically significant infections or fevers of unknown origin in the infant(s).
e. Obtain this information if outcome has occurred.
f. Collect only for live birth outcomes.

4.6.2. Registration Process

Registry enrollment will be voluntary and may be initiated by pregnant women or by their HCPs, who are acting as data reporters to the registry. After informed consent is obtained from eligible women, the participant and/or her HCPs will complete the ***Registration Form*** and the initial HCP data collection forms and submit them to the registry. The registry will provide a variety of conventional means for reporters to communicate with and submit data to the registry, including telephone, facsimile, postal mail, and email. The registry will provide a professional contact center in the US and Europe for communication with and collection of data from participants and their HCPs. The registry will also maintain a website that will provide information about the registry to facilitate participant registration and will also provide tools (e.g., down loadable CRF pages) that will facilitate the collection of accurate data.

The following information will be collected at registration.

Reporter Information

- Contact information for the participant as well as two alternate contacts outside the home to include name, address, phone number, and email address. This information will be verified and updated, as needed, at subsequent contacts with the participant.
- HCP reporter contact information

Maternal Information

- Maternal demographics
- Selected maternal medical history
- Previous registry participation
- Previous belimumab clinical trial participation
- Last menstrual period (LMP)
- Estimated date of delivery (EDD) determined from LMP
- Corrected estimated date of delivery (CEDD) (e.g., by ultrasound) if available
- Height
- Pre-pregnancy weight

Maternal Obstetrical History

- Number of previous pregnancies
- Outcome of previous pregnancies: live births, term births, preterm births, stillbirths, neonatal deaths, spontaneous miscarriages, elective terminations, ectopic pregnancies, and molar pregnancies
- History of offspring with birth defects
- Selected maternal conditions in previous pregnancies

- Prenatal imaging and aneuploidy screening/testing performed and findings including the identification of birth defects

Maternal SLE Disease Severity and Health Conditions within the 6 Months Prior to Conception and at Registration

- Baseline confirmation of SLE diagnosis by ACR criteria or clinical diagnosis
- Assessment for accrual of irreversible organ system damage by SDI
- Measurement of SLE disease activity by PGA
  If available:
  - Autoantibody testing results (anti-ds DNA, anti-cardiolipin antibodies, lupus anticoagulant, anti-Ro, anti-La)
  - Complement levels (C3/C4)
- Baseline assessment of proteinuria, serum and urine creatinine (urine protein/creatinine ratio preferred), (see Glossary)
- Other maternal conditions, e.g., thrombocytopenia and hypertension (see Glossary)
- Concomitant medications

Maternal Belimumab or other SLE treatment Exposure and Other Exposures (within 4 Months Prior to Conception and/or During Pregnancy)

- Belimumab or other SLE treatment course with dates of treatment. Dose and route of administration will be captured for belimumab exposed participants only.
  Tobacco, alcohol, and recreational drug use

4.6.3. Pregnancy Follow-up

Around the end of the second trimester and after pregnancy outcome, the ***Obstetrical Follow-up Form, Obstetrical Pregnancy Outcome Form*** (respectively) and ***Pediatric Outcome Form*** will be requested from the HCP. ***SLE treatment Prescriber*** data collection forms will also be requested from the HCP at these time points.

Information Collected at Interim Pregnancy Follow-up and Pregnancy Outcome

4.6.3.1. Follow-up at End of Second Trimester (~ 26 Weeks' Gestation)

Pregnancy Status

- Updates to EDD
- Subsequent prenatal imaging and aneuploidy screening/testing performed and findings including the identification of birth defects
- Pregnancy complications, if present
  - Pre-eclampsia/eclampsia (See Glossary)
  - Hypertension (See Glossary)

  - Diabetes mellitus: pre-gestational/gestational (See Glossary)
- Details of pregnancy outcome as described below if pregnancy is not ongoing

Maternal SLE Disease Severity and Health Conditions

- Measurement of SLE disease activity by PGA
  If available:
    - Autoantibody testing results (anti-ds DNA, anti-cardiolipin antibodies, lupus anticoagulant, anti-Ro, anti-La)
  - Complement levels (C3/C4)
- Updated assessment of proteinuria, serum and urine creatinine
- Concurrent medical conditions (update on changes during pregnancy)
- Concomitant medications

Maternal Belimumab or other SLE treatment Exposure and Other Exposures

- Belimumab or other SLE treatment course with dates of treatment. Dose and route of administration will be captured for belimumab exposed participants only.
- Tobacco, alcohol, and recreational drug use

4.6.3.2. Information Collected at Pregnancy Outcome

Maternal SLE Disease Severity and Health Conditions

- Measurement of SLE disease activity by PGA
  If available:
  - Autoantibody testing results (anti-ds DNA, anti-cardiolipin antibodies, lupus anticoagulant, anti-Ro, anti-La)
  - Complement levels (C3/C4)
- Updated assessment of proteinuria, serum and urine creatinine
- Concurrent medical conditions (update on changes during pregnancy)
- Concomitant medications

Maternal Belimumab or other SLE treatment Exposure and Other Exposures

- Belimumab or SLE treatment course with dates of treatment. Dose and route of administration will be collected for belimumab exposed participants only.
- Tobacco, alcohol, and recreational drug use

Pregnancy outcome

- Date of pregnancy outcome
- Pregnancy type (singleton, twin, triplet, other)

- Subsequent prenatal imaging and aneuploidy screening/testing performed and findings including the identification of birth defects
- Pregnancy outcome (e.g., live birth, stillbirth, neonatal death, spontaneous miscarriage, elective termination, ectopic pregnancy, molar pregnancy)

Fetal Outcome

- Fetal/infant characteristics (e.g., gender, birth weight, length, head circumference)
- Birth defect(s) and assessment of potential contributing factors
- For a fetal loss (spontaneous miscarriage, stillbirth, ectopic pregnancy, molar pregnancy), factors that may have had an impact on the fetal loss and attribution
- Serious and/or clinically significant infections in the infant
- Breastfeeding status (see Glossary)

4.6.4. Infant Follow-Up

Pediatric Follow-up forms will be requested from the pediatric HCP for live-born infants at approximately 4 and 12 months of age:

- Date of assessment
- Weight, length and head circumference of the infant at birth if not provided at pregnancy outcome (at 4 month assessment)
- Infant date of birth
- Current weight
- Developmental milestones
- Birth defects identified
- History of serious and/or clinically significant infections and/or fevers of unknown origin since last contact, causative microorganisms if available, treatment, and outcomes
- Breastfeeding status
- Mother's belimumab or other SLE treatment exposure post-partum, if dosed while breastfeeding

4.6.5. Targeted Follow-up Process

The Targeted Follow-up process will gather additional information, if required to assist data interpretation, on events and outcomes of interest including adverse maternal outcomes, birth defects, other adverse pregnancy outcomes, serious and/or clinically significant infections in infants, infant growth and developmental milestones. This additional information may include:

- Details of the specific outcome (e.g., birth defects, other adverse pregnancy outcomes, serious and/or clinically significant infections in infants, infant growth

and developmental milestones) may be requested from the reporting HCP on the ***Targeted Follow-up Form***

- Etiology of the specific outcome of interest
- Outcome attribution
- Lot number/s and expiry date/s of belimumab used to treat registry participants

4.6.6. Attempts to Obtain the Follow-Up Information

When follow-up is due for a registry participant, the HCP will be contacted and asked to provide follow-up information. Three subsequent attempts, as necessary, will be made approximately every 2 weeks through various modes of communication. If there is still no response from the HCP, a final communication will be sent indicating the case is lost to follow-up. If this communication prompts a response from the HCP, or from the participant or the requested data are later received at any point before the registry closes, the case will be re-opened and will no longer be considered lost to follow up. Once reopened, any data from assessments that had not been entered at the time the participant was lost to follow up (see Section 4.6.8.3) will be collected. If at any point in the follow-up process the reporter indicates that the participant is lost to follow-up, no further attempts will be made.

4.6.7. Follow-Up Process for Clarification of Information

If there are discrepancies in the data, the appropriate reporter(s) will be contacted for clarification. Three subsequent attempts, as necessary, will be made every 2 weeks. If no further information is obtained on an otherwise evaluable registry report (see Section 4.6.8.4), the discrepant information in the data fields may be left blank, identified as "unspecified." On a case-by-case basis, qualified registry staff or the principal investigator may make a determination on discrepant information (e.g., determination of partially illegible word or illogical year).

4.6.8. Registry Case Management and Disposition

4.6.8.1. Prospective Registry Reports

The registry will encourage prospective registration, which is defined as those exposures registered before the end of the pregnancy (i.e., live birth, fetal loss, etc). Two definitions for prospective reports of pregnancy will be used in this registry, traditional prospective and pure prospective [Holmes, 2008; Tomson, 2004]. Traditional prospective reports of pregnancy will include all women who enroll in the registry before the end of pregnancy (live birth, fetal loss, etc), regardless of known normal or abnormal prenatal test results. Pure prospective reports of pregnancy are a subset of traditional prospective reports and include those where (a) the enrollee did not know at the time of enrollment whether the fetus had a malformation, and (b) no prenatal testing was completed prior to enrollment. Reports of pregnancy defined as pure prospective will be included in the primary study population. Section 6 addresses the rationale, potential bias, and analytic techniques that may be employed to attempt to control for any known bias that may be introduced by this practice.

Prospective infant follow-up beyond the first year of life will not be routinely solicited by the registry but follow-up may be extended on a case-by-case basis if deemed medically necessary. In addition, while the study remains active, reports of birth defects that were identified in children after the 1st year of life and by 6 years of age will be entered into the database and reported in registry reports. This age criterion is consistent with CDC MACDP practice (see CDC MACDP Case Definition Criteria, 2015). Prospective reports of birth defects in infants beyond the first year of life and by 6 years of age will not be included in the primary study population, but will be described in the text of the registry final report. Prospective reports of infant infections beyond the first year of life will be forwarded to the sponsor for pharmacovigilance purposes only.

4.6.8.2. Retrospective Reports

Retrospective reports of pregnancy are those in which the pregnancy ended (live birth, fetal loss, etc) before enrollment or at the time of first contact with the registry. All retrospective cases reported to the registry will have data collected and entered into the database using the same procedures as prospective cases (traditional or pure); however, retrospective data will be summarized separately. Reports of pregnancy in which the pregnancy outcome or anticipated outcome is already known before enrollment can be biased toward the reporting of more unusual or severe cases compared to women whose pregnancy outcome is not yet known at the time of enrollment into the pregnancy registry. A woman or her HCP is more likely to notify the registry if a negative outcome is already known. Conversely, a woman or her HCP is less likely to notify the registry retrospectively if the pregnancy outcome was normal [Honein, 1999]. This potential enrollment bias could occur even for cases where the exposure information was obtained and documented in the medical record before the pregnancy outcome was known. Therefore, retrospective cases and traditional prospective cases will not be included in the primary study population, but will be summarized separately in interim and final reports to aid in detection of potential early signals. The frequency of birth defects in infants after the 1st year of life and by 6 years of age will be described in the text of the registry final report, stratified by traditional prospective, pure prospective and retrospective reports of pregnancy.

4.6.8.3. Lost to Follow-Up

For a prospective report or pregnancy where follow-up information on the pregnancy outcome, from a HCP, is never obtained, unavailable, and/or where the indication of a birth defect is designated as unknown, the pregnancy will be considered lost to follow-up. Cases lost to follow-up prior to pregnancy outcome will be tallied in the registry reports but not included in the primary study population. For infants, if pediatric follow-up information, from a HCP, is never obtained, unavailable, and/or where infant status is designated as unknown, the infant will be considered lost to follow-up. Any cases with infant outcome will be analyzed according to the length of infant follow up.

4.6.8.4. Evaluable Registry Reports

An evaluable registry report is a case with data submitted or confirmed by a HCP that meets the minimum criteria for a registry report, as described in Section 4.1, and for which the pregnancy outcome is known. Pure prospective reported evaluable cases will

be included in the primary study population section of the registry report. Evaluable belimumab exposed traditional prospective and retrospective cases as well as unexposed cases will be summarized separately in the interim and final reports. Participant-reported data without HCP confirmation will also be summarized separately in the final report.

4.6.8.5. Invalid Registry Reports

An invalid case is a report for which the minimum eligibility criteria are never obtained despite requests for the missing data. If the minimum data to determine eligibility are not provided initially, the case will be considered to be pending until all attempts to obtain missing data and requests for follow-up after the initial contact are complete. If after all attempts at follow-up are made, the minimum criteria for registration (detailed in Section 4.1) are still not met, the case will be considered invalid due to insufficient information. Invalid reports will not be included in the registry analyses.

4.6.8.6. Pregnancies in non-SLE Participants

This registry is intended to enroll participants with SLE. If a pregnancy is reported into the registry from a woman who has been exposed to commercially supplied belimumab within the 4 months prior to and / or during pregnancy but she is not diagnosed with SLE, the registry will collect that data. The data from such non–SLE pregnancies will be summarized separately from the pregnancies in participants with SLE. For non-SLE pregnancies, data in the CRF that are relevant to SLE but are irrelevant to the disease for which belimumab was prescribed will not be collected. As such, the data collection for maternal SLE disease severity will not be required for those participants.

4.7. Validation Procedures

Ensuring that the data obtained and delivered to GSK are of high quality will be an ongoing, multi-step process involving programming of edit checks for critical data variables in the data management system and visual review for completeness, logic, consistency, and accuracy. As recommended in regulatory guidance documents, case report forms will be carefully designed to ensure data quality and integrity. Participant-reported data will be verified by the appropriate HCP.

4.8. Endpoints and Data Analysis

This pregnancy registry will be a prospective cohort study and descriptive statistics will be calculated separately for traditional prospective and for pure prospective evaluable data for belimumab exposed participants. Data for belimumab exposed participants will be summarized separately from unexposed patients. In addition, data for participants having SLE will be summarized separately from participants not having SLE.

4.8.1. Belimumab Exposed Participants

The summary statistics for continuous and categorical variables to be used will be specified in the Reporting and Analysis Plan (RAP) but may include means, standard deviations, medians, minimums, maximums, percentiles, and percentages. Frequencies and proportions of adverse pregnancy outcomes, birth defects, and serious and/or

clinically significant infections in infants will be calculated along with their 95% confidence intervals.

The registry data will be used to conduct risk estimation and comparative analyses for the primary endpoint of birth defects and descriptive analyses for all secondary endpoints (i.e. pregnancy and infant outcomes). The presence of a birth defect will be summarized for registry participants with SLE who have been exposed to commercially supplied belimumab within the four months prior to and/or during pregnancy. The birth defect prevalence will be calculated as the percentage of birth defects from the total number of live births [Parker, 2010]; this approach is commonly used in other drug exposure pregnancy registries [Covington, 2004; Tomson, 2004; Holmes, 2008]. Fetal losses occurring at or after 20 gestational weeks with reported birth defects will be included in the estimation for the risk for birth defects to increase sensitivity and to allow comparison of the registry birth defect rates with the CDC MACDP and EUROCAT surveillance systems. An analysis will also be conducted to include fetal losses with reported birth defects occurring at less than 20 gestational weeks in the calculation of risk for birth defects.

Analyses will be stratified by subgroups of interest including: timing of exposure (i.e. prior to conception and after conception or during pregnancy as well as trimester or gestational week) and level of exposure (as indicated by dose and duration of belimumab dosing); gestational age at enrollment; maternal age; and region, such as North America and Europe. Additional details on subgroup analyses will be described in the RAP. Comparisons may be made to external cohorts, if appropriate.

Primary Endpoint:

- Birth defects

Secondary Endpoints:

Other pregnancy outcomes

- Spontaneous miscarriage
- Live birth (preterm birth and SGA)
- Stillbirth
- Elective termination

Infant outcomes through age 1 year

- Serious and/or clinically significant infections

4.8.2. Belimumab Analysis Population

The primary study population for which analyses will be presented includes pure prospective evaluable cases in participants having SLE considered exposed to commercially supplied belimumab (Section 4.4) that are not lost to follow-up (i.e., cases with appropriate outcome information that meet the minimum criteria for evaluation as specified in Section 4.1).

While the primary study population is pure prospective reported pregnancies, which can be used to ascertain actual population rates of events, the registry will complement its analyses by comprehensive review of other sources of information about pregnancy outcomes, including traditional prospective and retrospective reports.

4.8.2.1. Exclusions for Analysis Purposes

Invalid cases (Section 4.6.8.5), pregnancies deemed lost to follow-up, retrospective cases, cases where participants do not have SLE, and SLE patients not exposed to belimumab will be excluded from the primary belimumab study population.

4.8.2.2. Analysis Parameters for Birth Defects

Most structural defects originate in the first trimester of pregnancy, the period of organogenesis. Therefore, the outcome data for pure prospective evaluable cases will be stratified by the earliest trimester of exposure to belimumab. For this registry, gestational weeks will be estimated from the most reliable EDD as reported by the HCP. If a CEDD is provided by the HCP, it will be used instead. The date of conception will be calculated as the most reliable EDD minus 38 weeks. If the EDD is not available or never estimated, the first day of the LMP may be used to estimate gestational age. The second trimester begins at week 14 after the date of conception or LMP, and the third trimester begins at week 28.

Only cases meeting the CDC MACDP criteria for a defect or with 2 or more conditional defects will be included in the primary study population. Single minor defects do not constitute a birth defect according to the CDC MACDP classification; therefore, they will be listed in the report, but not included in the primary study population.

The birth defect primary analysis will include pure prospective pregnancies and a sensitivity analysis with traditional prospective pregnancies is planned.

4.8.2.3. Sequential Pregnancies

The number and outcome of sequential pregnancies will be noted and presented. Sequential pregnancies will be included in the analytic dataset unless they meet the exclusion criteria defined in Section 4.8.2.1.

4.8.2.4. Multiple Gestation Pregnancies

The number, type (e.g., twin, triplet), and outcome of multiple gestation pregnancies will be noted and presented. Multiple gestation pregnancies will be included in the analytic dataset unless they meet the exclusion criteria defined in Section 4.8.2.1.

4.8.3. Comparison Groups

The registry includes unexposed participants from the SABLE protocol, however, as the likely number of these participants will be small, formal comparisons of primary and secondary outcomes between belimumab exposed and unexposed participants will not be conducted.

Given the inherent difficulties in identifying a single optimal comparison cohort, several different cohorts may be used to provide background data for interpretation of data from the belimumab exposed participants in the pregnancy registry. This section describes these different cohorts, recognizing that one or more of these options may be implemented.

4.8.3.1. Population-Based Birth Defects Surveillance Programs

The Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) classification system will be used as the primary comparator data for defining and coding of birth defects for all registry sites. For the occurrence of birth defects, CDC MACDP data will be used for all sites as it is widely used as a comparator in pregnancy registries. The European Surveillance of Congenital Anomalies (EUROCAT) data will be used as a secondary comparison for European sites.

The primary objectives of CDC MACDP are to regularly and systematically monitor births of malformed infants to monitor changes in incidence or other unusual patterns and to develop a case registry for use in epidemiological studies. CDC MACDP actively searches for birth defects among the 50,000 annual births to residents of metropolitan Atlanta's 5 counties and abstracts medical records at all Atlanta obstetric hospitals, pediatric referral hospitals, genetics laboratories, and vital records [Correa-Villasenor, 2003]. CDC MACDP data have been used as a comparator cohort in examinations of birth defects for other pregnancy registries (acyclovir, sumatriptan, lamotrigine, and zidovudine) [Honein 1999]. The most recent CDC MACDP 5-year prevalence of 2.78% (6,945 cases with birth defects/249,999 live births) from 1999 to 2003 is deemed the most appropriate comparator birth defect data [Correa, 2007], due to lack of adequate birth defect data for the offspring of SLE mothers.

The total prevalence of birth defects overall in EUROCAT (including fetal deaths and pregnancy terminations) from 2004-2008 was 2.33% (http://www.eurocat-network.eu/). EUROCAT is a European network of population-based registries, including 43 registries in 20 countries, and it covers 29% of the European population. It started in 1979 and includes 1.5 million births per year in Europe. Its primary objectives are to provide essential epidemiological information on congenital anomalies and to act as an information and resource center to individuals and public health professionals.

4.8.3.2. External Data Sources

The registry will explore the possibility of identifying other appropriate external comparator data and continue to review the published literature to obtain background data for the pregnancy and infant outcomes evaluated in this study. It is important to note that such studies may vary in methodology, ascertainment and classification of birth defects or other pregnancy outcomes, geographic location, sample size, and other factors that could affect any formal comparisons. Therefore, quantitative comparisons between the registry and external data may be difficult to interpret. Furthermore, principal investigators for some of these studies may have expectations regarding publications and collaboration on the use of data.

4.8.3.3. Qualitative Case Analysis

A qualitative analysis of cases will be evaluated for the emergence of unique birth defects or patterns of birth defects, if warranted by our observations.

4.8.4. Essential Analyses of Belimumab-exposed Participants

A confidence interval estimation approach will be employed to descriptively compare the outcomes observed in the belimumab exposed participants of the pregnancy registry to external data. Comparisons with external SLE cohort data will be based on the observed frequency in the pregnancy registry and associated lower 95% confidence interval limit. For this registry, power was calculated using the same confidence interval estimation approach.

4.8.4.1. Adverse Pregnancy Outcomes

The registry will identify the number of cases of spontaneous miscarriages, elective terminations, stillbirths, preterm births, and SGAs; proportions of these outcomes will be calculated with 95% confidence intervals (CIs). The denominator for the proportion of spontaneous miscarriages will be those pregnancies enrolled prior to the 20th week of gestation. Because the prevalence of spontaneous miscarriages in pregnancy registries is heavily influenced by the timing of registry enrollment [Roberts, 2009], the analysis of spontaneous miscarriages will be stratified by gestational age at enrollment. Because the prevalence of preterm birth and low birth weight is elevated in multiple gestations, these cases will be excluded from the analysis of preterm birth and / or low birth weight outcomes.

Categorization of variables for stratification, such as earliest trimester of exposure, maternal age at enrollment, and gestational age at enrollment, will be described in the RAP.

4.8.4.2. Birth Defects

The prevalence of birth defects reported to the registry will be calculated as the percentage of birth defects from the total number of live births. The differences between the observed registry birth defect rates and these comparators will be estimated along with 95% confidence intervals. Fetal losses with reported birth defects occurring at or after 20 gestation weeks will be included in the numerator of the estimate of risk for birth defects to increase sensitivity and to allow comparison post-outcome with the CDC MACDP and EUROCAT. The analysis will also be conducted including fetal losses with reported birth defects occurring at less than 20 gestational weeks in the calculation of risk. It is possible that the background birth defect rate in the overall population may be different from the birth defect rate in SLE patients. Accordingly, additional analyses using different appropriate external SLE comparator cohorts will also be performed.

4.8.4.3. Serious and/or Clinically Significant Infections in Infants

The frequency and proportion of infections in infants (as defined in Section 4.3.3) during the infant's first year of life and 95% CI will be calculated, with the number of live births

as the denominator. These frequencies and proportions will be tabulated by timing and level of exposure to belimumab, breastfeeding status and length of infant follow-up.

For all outcomes of interest, comparisons between the registry data and data from appropriate external comparison cohorts will be considered, if available.

4.8.4.4. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the evaluable registry population. Demographic and baseline characteristics will also be summarized for the registry population that is lost to follow-up and compared with the evaluable population to assess potential differences. These data will be reviewed for factors that could affect interpretations of comparisons with the external comparator cohort(s). Additional data including maternal age, previous pregnancy outcomes, pregnancy complications, concomitant medications, maternal concurrent medical conditions, SLE disease severity, maternal outcomes, and belimumab dosing will be summarized with simple descriptive statistics and data listings. Further details will be provided in the RAP.

4.8.5. Analyses for the unexposed group

Registry data will be used to produce data summaries for the primary endpoint of birth defects and descriptive analyses for all secondary endpoints (i.e. pregnancy and infant outcomes) for the unexposed group. The unexposed group will be treated as an aggregate exposure grouping, i.e. no analyses are planned by specific medication. Patients in the unexposed group may have had prior exposure to belimumab during the course of the SABLE protocol but were not exposed to belimumab within 4 months or during pregnancy; these patients may be analysed separately if sample size is sufficient.

While the number of unexposed pregnancies from the SABLE cohort is expected to be low, these pregnancies may be informative in exploring any potential signals. For example, if a unique anomaly is observed in both the exposed and unexposed cohorts, this finding may suggest an etiology other than belimumab exposure.

4.8.6. Data Handling Conventions

Data will be managed with an electronic database, which is 21 CFR Part 11 compliant. The database will be backed up as part of the routine back-up process. The server will be backed up to tape daily as an incremental back-up (i.e., only files with changes since the last back-up will be backed up). A full back-up of the database will be performed weekly and stored securely off-site for 1 year. One full back-up per month will be stored off-site for 3 years; however, every 6 months back-ups will be stored for the duration of the registry. The Contract Research Organization will be responsible for retaining back-ups of the electronic database for the duration of the registry. On termination of all registry activities, the database and all electronic and paper files will be transferred to GSK for archiving.

5. SAMPLE SIZE AND POWER/PRECISION CALCULATIONS

This registry will be descriptive and will seek to enroll approximately 500 traditional prospective pregnancies exposed to commercially supplied belimumab. Research indicates that approximately 83-95% of pregnancies enrolled in pregnancy exposure registries will result in a live birth [Covington, 2010] and approximately 20-25% will be lost to follow-up [Covington, 2007], resulting in an upper estimate of 380 live births and a lower estimate of 311 live births.

The study design will allow the birth defect prevalence in belimumab-exposed participants to be estimated with an exact 95% confidence interval (CI) of (1.32%, 5.09%) assuming 350 live births and an observed belimumab birth defect prevalence equivalent to the MACDP general population birth defect prevalence of 2.78%. It needs to be further determined which, if any, external data sources may provide appropriate comparison data for the different outcomes evaluated in this pregnancy registry.

The registry acknowledges the challenges of enrolling this number of exposed live births and will carefully monitor enrollment trends and outcomes. This will be an open registry with initiation of participant recruitment in participating countries from the time of launch. Recruitment will continue with periodic reports filed to global regulatory agencies until the accumulated sample size is deemed adequate.

6. STUDY LIMITATIONS

Since participation in the registry will be voluntary, registry participants may not be representative of the overall SLE pregnant population. The most appropriate external comparator data and published literature available may be used to assist the interpretation of pregnancy registry outcome data. Care will be taken during data interpretation since external data may differ from registry data with regard to factors other than belimumab exposure. These factors may include the population under study, SLE clinical characteristics and disease severity, medications used to treat SLE, concomitant medical conditions, data source or collection methods, etc. thus potentially confounding any reported associations. Detailed data on such potential confounders may not be available, especially for any identified external cohorts, and hence it may be difficult to employ adjustment methodologies in the analysis.

The primary study population of belimumab exposed participants will include pure prospective pregnancies (i.e. (a) enrollee did not know at the time of enrollment whether the fetus had a malformation, and (b) no prenatal testing was completed prior to enrollment). Sensitivity analyses will be conducted with traditional prospective pregnancies comprised of women who enroll in the registry prior to the end of pregnancy (live birth, fetal loss, etc), regardless of known normal or abnormal prenatal test results.

While the primary analysis population in this registry will be limited to pure prospective reports, some belimumab-exposed pregnancies will be reported to the registry after the pregnancy ended (i.e. live birth, fetal loss, etc or retrospective reports) or following notification of an abnormal prenatal test result (included in traditional prospective

reports). In general, reports made to the registry after the pregnancy has ended and/or notification of an abnormal prenatal test result are biased toward reporting of the severe and unusual cases and are not reflective of the general experience with the medication. Moreover, information about the total number of exposed persons is not known. Therefore, rates of outcomes cannot be calculated from these data. However, a series of reported birth defects can be evaluated to detect patterns of specific birth defects and can assist with identification of potential early signals of therapy risks.

As reporting of pregnancies will be totally voluntary, it is possible that even in pure prospective reported cases, potential bias could exist. For example, high-risk pregnancies or low-risk pregnancies may be more likely to be reported.

Those pregnancies that have reached EDD, but for which pregnancy outcome information was unobtainable after multiple attempts, will be considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in follow-up procedures across countries and individual reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases the losses to follow-up may have on the analysis. However, efforts to compare some of the characteristics of each cohort may be conducted in an attempt to address this potential source of bias.

Fetal losses for which no birth defects have been reported may introduce misclassification bias. The percentage of these pregnancies consisting of potentially normal outcomes or birth defects is unknown. The data collection form will attempt to obtain information on birth defects detected at the time of the outcome. However, the reporting physician may not know the condition of the miscarried fetus.

7. STUDY MANAGEMENT

7.1. Ethical Approval

Institutional Review Board (IRB)/Ethics Committee (EC) approval or notification will be obtained or performed, respectively, in countries where this is required.

7.2. Informed Consent Process

Participant informed consent is required for participation in this pregnancy registry. Under applicable regulations in the US and several European countries, signed informed consent may be waived and verbal informed consent allowed.

Adults

Eligible adults who wish to participate in the registry will be asked to provide informed consent. Signed informed consent will be obtained in countries where it is required by local laws and regulations. In certain countries, the registry may qualify for verbal informed consent or waiver of documentation of signed informed consent (obtained by the process described below).

To facilitate verbal informed consent, registry coordinating center staff or the participant's HCP will review the Participant Information Sheet Consent Form with the pregnant woman (candidate registry participant) by telephone. The candidate registry participant is given an opportunity to ask questions and have them answered. If the candidate participant still wishes to participate in the registry, she provides verbal consent. This verbal consent is documented by registry coordinating center staff who forwards the registry participant a letter stating that she has provided verbal consent for registry participation together with a copy of the Participant Information Sheet/Consent form reviewed with the participant.

Minors

Minors are defined as individuals who have not attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in the countries in which the registry is being conducted. Belimumab is not approved for treatment of minors. However, if a minor requests to participate in the registry, the registry will permit this participation, if all eligibility criteria are met and on acquisition of assent from the minor and signed written consent from the parent or guardian. Written consent from both parents and/or guardians will be obtained in the US states and other countries, if this is required by local laws and regulations.

At the initial screening with potential participants, the registry associate will obtain consent to collect basic information about the individual, such as age and state or country of residence to determine whether the individual is a minor and to ensure that applicable local laws and regulations are followed.

7.2.1. Waiver of Signed Informed Consent for Registry participants in the US

Eligible adults in the US who wish to participate in the registry will be asked to provide verbal informed consent. The following US regulations indicate that waiver of signed informed consent should be appropriate for this registry in the US.

As stated in the US Code of Federal Regulations (CFR) 21 CFR 56.109 (and additionally in 45 CFR 46.117(c)(2)):

> "(c) An IRB shall require documentation of informed consent in accordance with 50.27 of this chapter, except as follows:
>
> (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subjects legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or
>
> (2) The IRB may, for some or all subjects, find that the requirements in 50.24 of this chapter for an exception from informed consent for emergency research are met.

> (d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research."

The research will involve no more than minimal risk to the subjects. This will be an observational study that involves no experimental intervention and poses no possibility of physical harm. The only potential risk will be a breach of confidentiality, and the registry will have well-established procedures in place to prevent any such breach of confidentiality. Extensive safeguards will be in place to ensure that participants' privacy is protected:

- An adequate plan is provided to protect the identifiers from improper use and disclosure (see Section 7.3).
- An adequate plan is provided to remove the identifiers at the earliest opportunity.
- Adequate assurances are provided that the protected health information will not be reused or disclosed to any other person or entity.

The research will involve no procedures for which written consent is normally required outside the research context. Enrollment in this observational study will be strictly voluntary. The schedule of participant visits and all treatment regimens will be at the complete discretion of the treating HCP. Data submitted to the registry will be limited to data routinely collected and documented in the participant's medical record.

7.2.2. Release of Participant Medical Information to the Registry

In order to collect data from the participant's health care providers and her newborn's pediatric health care provider, registry participants in all countries must complete medical release forms for each clinician who will report data to the registry.

7.2.2.1. Exemption of HIPAA Authorization for Registry Participants in the US

As a post-marketing safety reporting activity, this registry meets the criteria outlined below and should therefore be exempt from the US HIPAA Authorization as specified in 45 CFR 164.512 (b)(iii) which states:

> "(iii) A person subject to the jurisdiction of the Food and Drug Administration (FDA) with respect to an FDA-regulated product or activity for which that person has responsibility, for the purpose of activities related to the quality, safety or effectiveness of such FDA-regulated product or activity. Such purposes include:
>
> a. To collect or report adverse events (or similar activities with respect to food or dietary supplements), product defects or problems (including problems with the use or labeling of a product), or biological product deviations;
>
> b. To track FDA-regulated products;
>
> c. To enable product recalls, repairs, or replacement, or lookback (including locating and notifying individuals who have received

products that have been recalled, withdrawn, or are the subject of lookback); or

d. To conduct post marketing surveillance;"

e. To further clarify this issue, an article published by the Pregnancy Labeling Task Force, US FDA, states:

"…the HIPAA Privacy Rule specifically permits the disclosure of protected health information by covered entities such as physicians or hospitals for public health purposes related to the quality, effectiveness and safety of FDA-regulated products to both the manufacturers and directly to the FDA. This includes collecting or reporting adverse events, tracking FDA-regulated products and conducting post-marketing surveillance to comply with requirements or at the direction of the FDA." [Kennedy, 2004.]

7.2.2.2. Release of Medical Information to the Registry Outside of the US

For all countries outside of the US, the registry will comply with local laws and regulations to facilitate release of participant medical information to the registry.

7.3. Participant Confidentiality

Each participant's identity will be known only to the third-party contractor (Registry Coordinating Center), the registry site, enrolling individual (i.e., participant or HCP), and relevant HCPs (i.e. belimumab prescriber, obstetrician, pediatrician). The registry will assign participant and infant identification numbers, which will be used to identify registry participants and their infant offspring. The dataset used in each analysis of data from the registry will contain coded registry participant identifiers only for both the pregnant mothers and infants.

Regulatory authorities, or GSK approved auditors, may inspect the registry data files which may include personal identifier information of registry participants.

7.4. Reporting of Adverse Drug Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event), and adverse events associated with circumstances of Overdose whether accidental or intentional, Medication Errors, Abuse or effects of drug withdrawal, or Misuse.

For both belimumab exposed and unexposed participants, serious adverse events (SAEs) will be defined as those adverse events that result in death, are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; result in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. In addition,

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 is considered a SAE. Adverse events (AEs), if reported, will be recorded on registry data collection tools as part of registry data collection (and considered 'solicited' for regulatory reporting purposes).
If an AE is considered serious by the reporter, a SAE Report Form will be completed. All SAEs will be entered into the registry database and forwarded to GSK within 1 business day of registry notification. In addition, any other adverse pregnancy outcomes will also be reported to GSK within 1 business day of registry notification.

GSK will then forward all AE information to regulatory agencies as required by applicable regulations. The registry will follow industry guidance [FDA, 2002; EMEA, 2005] for regulatory reporting of adverse pregnancy outcomes and serious infections experienced by the infants.

7.5. Study Closure/Uninterpretability of Results

In accordance with industry guidance [FDA, 2002], the registry could consider discontinuation at any of the following times:

- Sufficient information has accumulated to meet the scientific objectives of the registry
- 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

Prior to discontinuing this registry, the regulatory authorities will be consulted, as appropriate.

7.6. Study Milestones

This registry is intended to be available for initiation of recruitment in participating countries from the time of launch following acquisition of market authorization. Recruitment will continue until the criteria described in Section 5 have been achieved. Study close-out and final reporting activities will be initiated on completion of the pregnancy outcome and infant follow-up on the last participant in the registry.

7.7. Study Sponsor

This study will be conducted by GSK. GSK will sponsor the study in all countries. GSK will lead on the operational conduct of the registry worldwide working with the Contract Research Organization.

7.8. Central Registry Sites/Principal Investigators

Each country participating in the registry will have a central registry site and principal investigator who will be responsible for the following tasks:

- Submitting protocol for IRB/EC approval
- Promoting the registry among interested physicians and medical societies and assisting in developing and nurturing a national network of physicians who will report data to the registry
- Assisting in registry awareness activities
- Coordinating and facilitating enrollment of eligible participants into the registry and collecting follow-up data
- Assisting in assessment of case report form data submitted from reporters and in resolution of data queries
- Transferring data to the Registry Coordinating Center

Any HCP caring for eligible pregnant women may participate in the registry. Interested HCPs should contact the central registry site or Registry Coordinating Center to participate.

7.9. Registry Coordinating Center

The Registry Coordinating Center will be responsible for the overall daily management of the registry and facilitating all data collection and management activities. The Registry Coordinating Center will be responsible for the following tasks:

- Assisting the sites in submitting the registry protocol for IRB and EC approval
- Assisting the sites in promoting the registry among interested physicians and medical societies, and assisting in developing and nurturing a national network of physicians who will report data to the registry
- Assisting in all other registry awareness activities
- Assisting the sites in facilitating enrollment of eligible participants and collecting follow-up data
- Assessing case report form data submitted from reporters and resolving data queries
- Entering, managing, and analyzing data
- Updating the registry interim and final reports
- Overseeing the activities of the sites
- Ensuring that all case reports of serious adverse events and all adverse pregnancy outcomes are forwarded to GSK within 1 business day of registry notification for regulatory reporting requirements and entered into the registry database

- Ensuring that all follow-up data, that are attainable from HCPs, on serious adverse events and all adverse pregnancy outcomes are forwarded to GSK within 1 business day of receipt and entered into the registry database
- Contributing to the scheduling and planning of the registry Scientific Advisory Committee (SAC) meetings and participation in SAC meetings

7.10. Scientific Advisory Committee

The SAC will consist of selected global experts such as those specializing in the treatment of SLE, maternal and fetal medicine, teratology, epidemiology/biostatistics, pediatrics, and representatives from GSK (clinical, statistics, epidemiology). The SAC will be responsible for supervising the data collection and analysis; however, these activities will be performed by an independent external group that is experienced in the conduct and operations of registries. The SAC will be expected to meet at least annually to perform an independent review of the data collected, including review and classification of reported birth defects, and to carry out any actions required, including review and interpretation of interim data analyses and reports and publications of registry data. The SAC may meet on ad hoc occasions if indicated. In addition to the above activities, the SAC may design and implement strategies to heighten awareness of the registry.

An expert in teratology will be included in the SAC and will act as the birth defect evaluator for the registry. His/her responsibilities will include the review, evaluation, and classification of reports of birth defects. Additionally, the birth defect evaluator will provide an opinion regarding the possible temporal association of the belimumab exposure or other SLE treatment exposure to the development of observed defects.

7.11. Birth Defect Monitoring and Signal Generation

The intent of the registry is to identify potential signals that may indicate an increased risk of major birth defects in the offspring of women following exposure to belimumab during pregnancy. Therefore, it will be necessary to monitor the cumulative data to detect potential signals or patterns, to evaluate them, and to determine the necessary course of action if a signal is generated. The registry may never have sufficient power to detect an increased risk for a particular rare outcome to belimumab. However, the registry has adopted a plan developed by the Antiretroviral Pregnancy Registry for determining what constitutes a signal for a birth defect, how it is reviewed, and what action might be taken should such a signal be seen [Covington, 2004]. For example, the "Rule of Three" convention specifies that once 3 similar birth defects have accumulated with any specific exposure, these cases are flagged for immediate review. The likelihood of finding 3 of any specific defects in a cohort of <600 by chance alone is less than 5% for all but the most common defect classes (i.e., those occurring with the rate of <1/700). To enhance the insurance of prompt, responsible, and appropriate action in the event of a potential signal, the registry will employ the strategy of "threshold" based on the Council of International Organizations for the Medical Sciences [CIOMS, 1999]. The threshold for action will be determined by the extent of certainty about the cases and tempered by the specifics of the cases.

The unexposed cases and those exposed to other SLE treatments will be reviewed and used in evaluating potential belimumab signals.

In addition, the evaluator will review all birth defects in aggregate to identify any possible patterns reported. Should a potential pattern occur, it will be discussed at the SAC meetings. However, if at any time a discussion prior to the meeting is deemed necessary, an additional meeting may be scheduled. If a potential signal is identified, the component cases may be evaluated individually to determine if there is cause for concern.

On an ongoing basis, the registry and associated experts will review all reports of birth abnormalities individually and cumulatively for potential signals that are generated in the collection of this information.

The SAC will develop signal generation criteria regarding serious and/or clinically significant infections in infants as considered appropriate.

7.12. Registry Awareness Activities

To promote awareness, the registry will actively reach out to HCPs treating women with SLE. HCPs will be made aware of the registry through a variety of means and venues, which may include the following:

- Enlisting the aid of the registry principal investigator in each country as well as GSK Medical Science Liaisons (MSLs) and SAC members to spread the knowledge to other physicians about the registry
- Collaborating with belimumab prescribers as well as investigators who are involved in a clinical trial or post marketing SLE studies, including the SABLE protocol. Collaborating with other groups, e.g., Systemic Lupus Erythematosus International Collaborating Clinics, British Isles Lupus Assessment Group, and Lupus Clinical Trials Consortium
- Communicating with lupus patient associations in North America and in Europe
- Enlisting the aid of Food and Drug Administration (FDA), CDC, and other relevant organizations to facilitate recruitment
- Notifying applicable organizations for posting on their Web sites, i.e., FDA, clinicaltrials.gov, centerwatch.com, GSK sites
- Including registry contact information in the package insert, if permitted, in accordance with local regulations
- Including information about the registry in selected promotional materials directed to HCPs and consumers (e.g. advertisements, product websites, patient education brochure)
- Distributing registry interim data reports to HCPs

- Distributing a comprehensive informational kit to HCPs to make them aware of the registry
- Distributing personal mailings to applicable HCPs
- Presenting at applicable scientific and/or clinical meetings

7.13. Study Reporting and Publications

An interim data report will be generated at least annually; this will summarize the study status and the cumulative data on the registry to date including information on the primary and secondary endpoints. At the planned end of the registry, a final report will be generated. The comprehensive, RAP-specified final report will contain the background, study design, including countries where participant recruitment is occurring, and the full analysis plan.

PBRER and the final registry report will be submitted to the relevant regulatory authorities and the most recent interim report of registry data will be available to HCPs on a publicly accessible registry Web site. Ad hoc data summaries will be generated if indicated by agreement with the SAC.

The study sponsor, GSK, will seek to publish the data from the belimumab pregnancy registry study in searchable peer-reviewed scientific literature, aiming to publish and present the data in the most reputable peer-reviewed journals and scientific meetings possible. Data from the registry study will be submitted for publication within 18 months of completion of the final registry analysis. GSK will determine authorship of any publications resulting from this study in accordance with the authorship criteria of the International Committee of Medical Journal Editors [ICMJE, 2010], or, if more stringent, the criteria of an individual journal. Publication plans (covering manuscripts, abstracts, posters and presentations) will be agreed upon and developed in collaboration between the study sponsor and named authors. All publications (e.g., manuscripts, abstracts, oral/slide presentations) based on this study must be submitted to GSK allowing at least 30 days for review. Data are the property of GSK and cannot be published without prior authorization from GSK.

7.14. Resourcing Needs

This study will be outsourced to a Contract Research Organization who will perform data collection, data management, and data analysis under the guidance of GSK.

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9. GLOSSARY

Term	Registry Definition
Birth defect	The registry defines a birth defect as any major structural or chromosomal defect or 2 or more conditional defects in live-born infants, stillbirths, or fetal losses of any gestational age (including outcomes prior to 20 weeks' gestation or weighing <500 g). This definition is consistent with but not restricted to the CDC MACDP definition.
Breastfeeding	Providing mother's own milk for infant nutrition
Conditional defect	The registry defines a conditional defect as a condition which appears in the MACDP Exclusion List.
Corrected EDD	Estimated date of delivery obtained by prenatal test (e.g., ultrasound) when the LMP is unknown or deemed to be unreliable for estimating gestational age.
Date of conception	Calculated as the most reliable EDD minus 38 weeks.
Eclampsia	A life-threatening condition of pregnancy following pre-eclampsia characterized by seizures that are unrelated to a preexisting brain condition.
Ectopic pregnancy	Implantation of a conception outside of the uterus.
Elective termination	Voluntary interruption of pregnancy prior to natural outcome. Includes pregnancy termination that occurs electively, to preserve maternal health, or due to fetal abnormalities. Terminology may include elective abortion, therapeutic abortion, artificial abortion and induced abortion.
End of pregnancy	Defined as live birth, fetal loss (i.e. spontaneous miscarriage, stillbirth, ectopic pregnancy, molar pregnancy), etc.
Estimated due date (EDD)	The calendar date upon which it is estimated that the baby will be born, calculated as the LMP + 40 weeks.
European Surveillance of Congenital Anomalies (EUROCAT)	A network of population-based registries for the epidemiologic surveillance of congenital anomalies that began in 1979. Currently it includes 43 registries in 20 countries and covers 29% of the European birth population. It is a resource for the development of uniform methods and approaches to birth defect surveillance.
Fetal loss	Defined as spontaneous miscarriage, stillbirth, ectopic pregnancy, molar pregnancy

Term	Registry Definition
Gestational diabetes	Any degree of glucose intolerance with onset or first recognition during pregnancy.
Gestational hypertension	The development of high blood pressure after 20 weeks of pregnancy; this condition is not associated with proteinuria or other signs of pre-eclampsia and may also be known as pregnancy-induced hypertension.
Hypertension	Elevated blood pressure described as systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg.
Last menstrual period (LMP)	The first day of the last menstrual period prior to conception.
Maternal death	The death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.
Metropolitan Atlanta Congenital Defects Program (MACDP)	A program that monitors all major birth defects in 5 counties of the metropolitan Atlanta area (Clayton, Cobb, DeKalb, Fulton and Gwinnett) with approximately 50,000 annual births from a population of about 2.9 million. MACDP acts as the model for many state-based programs and as a resource for the development of uniform methods and approaches to birth defect surveillance.
Molar pregnancy	A conception that results in a gestational trophoblastic tumor.
Neonatal death	An infant who after live birth expired within the first 28 days of life.
Pre-eclampsia	A condition of pregnancy occurring after 20 weeks gestation characterized by hypertension, edema, and proteinuria
Preterm birth	An infant born at gestational age <37 weeks
Prenatal test	Diagnostic or screening evaluations that may give insight into the outcome of the pregnancy. Examples include ultrasound, amniocentesis, chorionic villus sampling, nuchal translucency testing, and maternal serum screening for aneuploidy or neural tube defects.

Term	Registry Definition
Proteinuria	The presence of excess protein in the urine. Proteinuria is typically assessed by urine dipstick (graded as trace or + (low) vs ++ to ++++ (medium-high)), or urine biochemistry on a spot urine (protein/creatinine ratio >30), or a 24 hour urine collection (300 mg protein/24 hours).
Pure prospective report	Pure prospective reports of pregnancy are a subset of traditional prospective reports and include those where (a) the enrollee did not know at the time of enrollment whether the fetus had a malformation, and (b) no prenatal testing was completed prior to enrollment.
Retrospective report	Retrospective reports of pregnancy are those in which the pregnancy ended before enrollment or at the time of first contact with the registry.
Small for Gestational Age (SGA)	Defined as an infant whose birth weight is less than the 10th percentile for the gestational age. The registry will utilize the sex specific international growth reference standards from the INTERGROWTH-21st group (Villar, 2014) for those born at ≥33 weeks GA and also those endorsed by ACOG (Alexander, 1996) for all infants of all gestational ages.
Spontaneous miscarriage	Fetal death or expulsion of products of conception prior to 20 weeks' gestation. Terminology may include missed abortion, blighted ovum, incomplete abortion, and inevitable abortion.
Stillbirth	A fetal death occurring 20 weeks' gestation or greater, or if the gestational age is not available, weighing 500 g or more.
Temporality assessment	The determination of the probable association or non-association of the timing of the maternal exposure in pregnancy relative to the probable timing of organogenesis of a defect.
Term birth	An infant at outcome ≥37 weeks' gestational age, or if gestational age is not available, weighing ≥2,500 g.

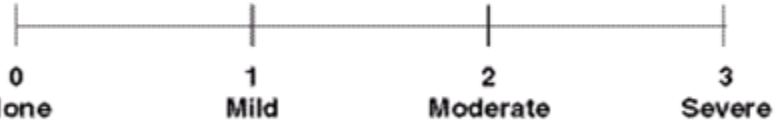
Term	**Registry Definition**
Thrombocytopenia	A decreased number of platelets in the blood associated with an increased risk of bleeding. A peripheral blood platelet count greater than 150,000/ mm^3 is considered normal, 50,000 - 150,000/mm^3 is consistent with mild to moderate thrombocytopenia, and less than 50,000/mm^3 is consistent with severe thrombocytopenia.
Traditional prospective report	Traditional prospective reports of pregnancy will include all women who enroll in the registry before the end of pregnancy (live birth, fetal loss, etc), regardless of known normal or abnormal prenatal test results.

10. LIST OF APPENDICES

10.1. Appendix 1: PHYSICIAN'S GLOBAL DISEASE ASSESSMENT

PHYSICIAN'S GLOBAL DISEASE ASSESSMENT

How do you assess your patient's current disease activity?



Adapted from: Petri M, Hellman D, Hochberg M. Validity and reliability of lupus activity measures in the routine clinical setting. J Rheumatol 1992;1992:53-9.

10.2. Appendix 2: SLICC/ACR Damage Index

Systemic 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/24 hours	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)

*Damage (nonreversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

Adapted from: Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363-9.

10.3. Appendix 3: Protocol Amendment 01 Changes

Protocol Amendment 01 applies to all countries and sites.

Protocol GlaxoSmithKline Document Number 2010N108011_00 was amended. Detailed descriptions of substantive changes to the protocol are listed below. Additional administrative and minor typographical/editorial changes have also been made.

Section(s)	Previous Wording	New Wording	Rationale
Protocol Summary: Statistical/ Analytical Methods	Descriptive statistics will be performed for all prospective, evaluable data. The summary statistics for continuous and categorical variables to be used will be specified in the Reporting and Analysis Plan (RAP) but may include means, standard deviations, medians, minimums, maximums, percentiles, and percentages. Frequencies and proportions of adverse pregnancy outcomes, birth defects, serious and/or clinically significant infections in infants will be calculated with corresponding 95% confidence intervals.	Descriptive statistics will be performed for all prospective, evaluable data. The summary statistics for continuous and categorical variables to be used will be specified in the Reporting and Analysis Plan (RAP) but may include means, standard deviations, medians, minimums, maximums, percentiles, and percentages. Frequencies and proportions of adverse pregnancy outcomes, birth defects, serious and/or clinically significant infections in infants will be calculated with corresponding 95% confidence intervals. **For the primary endpoint of birth defect prevalence, the estimates of birth defect prevalence from MACDP and EUROCAT will be used to represent external population comparators. The differences between the observed registry birth defect rates and these comparators will be estimated along with 95% confidence intervals.**	Clarify planned statistical/analytical methods for the primary endpoint
4.2 Study Design	The registry will collect data that are routinely documented in the participant's medical record in the course of usual care, with the possible exception of the Physician Global Assessment (PGA) of SLE disease activity	The registry will collect data that are routinely documented in the participant's medical record in the course of usual care, with the possible exception of the Physician Global Assessment (PGA) of SLE disease activity **(Appendix 1) and the SLICC/ACR Damage Index (SDI;**	Assessment of SDI at registration has been added; this will aid in controlling for confounding by indication in the analyses

Section(s)	Previous Wording	New Wording	Rationale
		Appendix 2).	
4.6 Data Collection and Management	Only data acquired during the course of routine medical care will be collected, with the possible exception of the PGA of SLE disease activity	Only data acquired during the course of routine medical care will be collected, with the possible exception of the PGA of SLE disease activity (**Appendix 1) and the SDI (Appendix 2)**	Assessment of SDI at registration has been added; this will aid in controlling for confounding by indication in the analyses
4.2 Study Design, 4.6 Data Collection and Management	No previous text	**The SDI records irreversible organ system damage occurring in participants with SLE regardless of etiology. Damage may be attributed to active SLE disease, concomitant medication or intercurrent illness [Gladman, 1996]**	Description for the SDI that was added to the protocol as another measure of disease severity
4.6.2 Registration Process	*Maternal SLE Disease Severity and Health Conditions within the 6 Months Prior to Conception and at Registration* • Baseline confirmation of SLE diagnosis by ACR criteria or clinical diagnosis • Measurement of SLE disease activity by PGA	*Maternal SLE Disease Severity and Health Conditions within the 6 Months Prior to Conception and at Registration* • Baseline confirmation of SLE diagnosis by ACR criteria or clinical diagnosis • **Assessment for accrual of irreversible organ system damage by SDI** • Measurement of SLE disease activity by PGA	Assessment of SDI at registration has been added to the protocol as another measure of baseline disease severity
4.6.8.1 Prospective Registry Reports	The registry will encourage prospective registration, which is defined as registration of a pregnancy exposure prior to knowledge or perceived knowledge of the pregnancy outcome (eg, structural defect or genetic abnormality noted on a prenatal test). Those with no abnormalities identified on a prenatal test prior to enrollment will be considered prospective and included in the analysis.	The registry will encourage prospective registration, which is defined as **those exposures registered before the outcome of pregnancy is known (e.g.,** structural defect or genetic abnormality noted on a prenatal test). Those with no abnormalities identified on a prenatal test prior to enrollment will be considered prospective and included in the analysis**, while women who are still pregnant but with a reported fetal abnormality at the time of enrollment are**	Clarification on the definition for prospective reports of pregnancy compared to retrospective reports of pregnancy

Section(s)	Previous Wording	New Wording	Rationale
		considered "retrospective" reports.	
4.6.8.2 Retrospective Reports	Retrospective reports will be defined as those cases for which the pregnancy outcome was known or an abnormality had been identified before enrollment. All retrospective cases reported to the registry will have data collected and entered into the database using the same procedures as for prospective cases, however, these retrospective data will be summarized separately. Retrospective reports can be biased toward the reporting of more unusual or clinically significant pregnancy outcomes and are less likely to be representative of the general population experience than cases reported prior to knowledge of the outcome [Honein 1999].	Retrospective reports will be defined as those **received after the outcome or anticipated outcome of pregnancy is known** before enrollment. All retrospective cases reported to the registry will have data collected and entered into the database using the same procedures as for prospective cases, however, these retrospective data will be summarized separately. **Inclusion of retrospective reports, in which the pregnancy outcome is already known before enrollment,** can be biased toward the reporting of more unusual **and severe cases** and are less likely to be representative of the **SLE population of women exposed during pregnancy, compared to women whose pregnancy outcome is not yet known at the time of enrollment into the pregnancy registry. A woman or her HCP is more likely to notify the registry if a negative outcome is already known. Conversely, a woman or her HCP is less likely to notify the registry retrospectively if the pregnancy outcome was normal. [Honein 1999]. This potential enrollment bias could occur even for cases where the exposure information was obtained and documented in the medical record before the pregnancy outcome was known.**	Clarification on the definition for prospective reports of pregnancy compared to retrospective reports of pregnancy

Section(s)	Previous Wording	New Wording	Rationale
Table 4-1 Summary Table of Evaluations, Section 4.6.3.2 Information Collected at Pregnancy Outcome, Section 4.6.4 Infant Follow-Up	No previous text	**Added row for evaluation of breastfeeding status for live births**	Clarification that lactation status refers to the mother and breastfeeding status refers to the infant.
4.8.1 Analysis Population	No previous text	**While the primary study population is prospectively reported pregnancies, which can be used to ascertain actual population rates of events, the registry will complement its analyses by comprehensive review of other sources of information about pregnancy outcomes, including retrospective reports.**	Clarification about the primary analysis population and additional analyses including analyses of retrospective reports of pregnancy
4.8.2.1 Comparison Groups	For the primary endpoint of birth defect prevalence, the estimates of birth defect prevalence from MACDP and EUROCAT **may** be used to represent external population comparators.	For the primary endpoint of birth defect prevalence, the estimates of birth defect prevalence from MACDP and EUROCAT **will** be used to represent external population comparators.	Provide more details about the analysis plan and approaches for comparative analyses
4.8.3 Essential Analyses	No previous text	**A confidence interval estimation approach will be employed to descriptively compare the outcomes observed in the pregnancy registry to external data. Comparisons with external SLE cohort data will be based on the observed frequency in the pregnancy registry and associated lower 95% confidence interval limit. For this registry, power was calculated using the same confidence interval estimation**	Provide more details about the planned analytical methods

Section(s)	Previous Wording	New Wording	Rationale
		approach.	
4.8.3.2 Birth Defects	The prevalence of birth defects reported to the registry will be calculated as the percentage of birth defects from the total number of live births. Fetal losses with reported birth defects occurring at or after 20 gestation weeks will be included in the numerator of the estimate of risk for birth defects to increase sensitivity and to allow comparison post-outcome with the CDC MACDP and EUROCAT. The analysis will also be conducted including fetal losses with reported birth defects occurring at less than 20 gestational weeks in the calculation of risk.	The prevalence of birth defects reported to the registry will be calculated as the percentage of birth defects from the total number of live births. **The differences between the observed registry birth defect rates and these comparators will be estimated along with 95% confidence intervals.** Fetal losses with reported birth defects occurring at or after 20 gestation weeks will be included in the numerator of the estimate of risk for birth defects to increase sensitivity and to allow comparison post-outcome with the CDC MACDP and EUROCAT. The analysis will also be conducted including fetal losses with reported birth defects occurring at less than 20 gestational weeks in the calculation of risk. **It is possible that the background birth defect rate in the overall population may be different from the birth defect rate in SLE patients. Accordingly, additional analyses using different appropriate external SLE comparator cohorts will also be performed.**	Clarify planned statistical/analytical methods for the primary endpoint
4.8.3.3. Serious and/or Clinically Significant Infections in Infants	The frequency and proportion of infections in infants (as defined in Section 4.3.3) during the infant's first year of life and 95% CI will be calculated, with the number of live births as the denominator. These frequencies and proportions will be tabulated by timing and level of exposure to belimumab, lactation status, and length of infant follow-up	The frequency and proportion of infections in infants (as defined in Section 4.3.3) during the infant's first year of life and 95% CI will be calculated, with the number of live births as the denominator. These frequencies and proportions will be tabulated by timing and level of exposure to belimumab, **breastfeeding status** and length of infant follow-up.	Clarification that lactation status refers to the mother and breastfeeding status refers to the infant.

Section(s)	Previous Wording	New Wording	Rationale
7.4 Reporting of Adverse Drug Events	Serious adverse events (SAEs) will be defined as those adverse events that result in death, are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; 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 SAEs other than adverse pregnancy outcomes or serious infection in the infant will be collected through an appropriate registry data collection tool. All SAEs will be entered into the registry database The registry will report the following to the GSK/HGS Safety Departments within 1 business day of registry notification, when considered to have a reasonable possibility of attribution to belimumab by the HCP: • Birth defects • All other adverse pregnancy outcomes • All serious infections experienced by the infants born to mothers in the registry • All other SAEs The GSK/HGS Safety Department will then forward all applicable adverse pregnancy outcomes and serious adverse events to the	Serious adverse events (SAEs) will be defined as those adverse events that result in death, are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; result in persistent or significant disability/incapacity; or **is a congenital anomaly/birth defect. In addition,** 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 **is considered a SAE. Adverse events (AEs), if reported, will be recorded on registry data collection tools as part of registry data collection (and considered 'solicited' for regulatory reporting purposes).** **If an AE is considered serious by the reporter, a SAE Report Form will be completed. All SAEs will be entered into the registry database and forwarded to the GSK/HGS Safety Departments within 1 business day of registry notification. In addition, any other adverse pregnancy outcomes will also be reported to the GSK/HGS Safety Departments within 1 business day of registry notification.** The GSK/HGS Safety Department will then forward all **AE information to regulatory agencies as required by applicable regulations. The registry will follow industry guidance [FDA, 2002; EMEA, 2005] for regulatory reporting of adverse pregnancy outcomes and**	Collection of all SAEs is no longer planned; revised operational procedures for AE reporting and definition for 'solicited' AE reports have been included. Specific maternal conditions that are known to impact pregnancy outcomes including, but not limited to, hypertension, thrombocytopenia, diabetes mellitus (pre-gestational or gestational) and pre-eclampsia will still be collected (including seriousness of event). This extent of safety data collection is in keeping with the objectives of a pregnancy registry.

Section(s)	Previous Wording	New Wording	Rationale
	regulatory authorities, as required by global regulations. The registry will follow industry guidance [FDA, 2002; EMEA, 2005] for regulatory reporting of adverse pregnancy outcomes and serious infections experienced by the infants. All other SAEs will be reported in accordance with local regulatory requirements.	**serious infections experienced by the infants.**	
10 Appendices	No previous text	**Added Appendix 1 and Appendix 2: PGA and SDI Instruments**	Provide sample instruments for standardized assessments that will utilized in data collection procedures

10.4. Appendix 4: Protocol Amendment 02 Changes

Protocol Amendment 02 applies to all countries and sites.

Protocol GlaxoSmithKline Document Number 2010N108011_01 was amended. Detailed descriptions of substantive changes to the protocol are listed below. Additional administrative and minor typographical/editorial changes have also been made.

Section(s)	Previous Wording	New Wording	Rationale
Protocol Summary: Study Population, 4.1 Study Population	Sufficient information to classify the pregnancy as prospective or retrospective (i.e., whether the outcome of pregnancy was known at the time of first contact with the registry).	Sufficient information to classify the pregnancy report as prospective or retrospective. **Retrospective reports of pregnancy are those in which the pregnancy ended before enrollment or at the time of first contact with the registry. Two definitions for prospective reports of pregnancy will be used in this registry, traditional prospective and pure prospective:** **Traditional prospective reports of pregnancy will include all women who enroll in the registry before the end of pregnancy (live birth, fetal loss, etc), regardless of known normal or abnormal prenatal test results** **Pure prospective reports of pregnancy are a subset of traditional prospective reports and include those where (a) the enrollee did not know at the time of enrollment whether the fetus had a malformation, and (b) no prenatal testing was completed prior to enrollment**	New definitions for reports of pregnancy (traditional prospective, pure prospective and retrospective) that will be utilized by the REGISTRY, as requested by the EMA. Traditional prospective reports of pregnancy include all women who enrolled before the end of pregnancy and pure prospective is a subset of traditional prospective pregnancies. Retrospective reports of pregnancy include women who enrolled after the pregnancy outcome or end of pregnancy (live birth, fetal loss, etc)
Protocol Summary: Number of Participants	The registry will seek to enroll approximately 500 prospective pregnancies.	The registry will seek to enroll approximately 500 prospective pregnancies **exposed to commercially supplied belimumab**.	Clarification about the type of prospective pregnancy for target enrollment

Section(s)	Previous Wording	New Wording	Rationale
Protocol Summary: Statistical/Analytical Methods	Descriptive statistics will be performed for all prospective, evaluable data.	Descriptive statistics will be **calculated separately for traditional prospective and for pure prospective** evaluable data.	Clarify planned statistical/analytical methods
4.2 Study Design	A retrospective pregnancy will be defined as a case for which the pregnancy outcome was known or an abnormality had been identified before enrollment. All retrospective cases reported to the registry will have data collected and entered into the database (as appropriate for the underlying disease) using the same procedures as for prospective cases; however, these retrospective cases will be summarized separately.	Retrospective reports of pregnancy will be defined as a case for which the pregnancy **ended (live birth, fetal loss, etc)** before enrollment **or at the time of first contact with the registry**. All retrospective cases reported to the registry will have data collected and entered into the database (as appropriate for the underlying disease) using the same procedures as prospective cases **(traditional or pure)**; however, retrospective cases will be summarized separately.	Clarification about the new definitions for reports of pregnancy
4.5 Adverse Drug Experiences/ Event Measures	Reports of serious adverse events in the mother or infant for which there is a definite or a reasonable possibility of attribution to belimumab	Reports of serious adverse events in the mother or infant	Clarification to align with Section 7.4 that was revised during protocol amendment01
4.6.8.1 Prospective Registry Reports	The registry will encourage prospective registration, which is defined as those exposures registered before the outcome of pregnancy is known (e.g., structural defect or genetic abnormality noted on a prenatal test). Those with no abnormalities identified on a prenatal test prior to enrollment will be considered prospective and included in the analysis, while women who are still pregnant but with a reported fetal abnormality at the time of enrollment are considered "retrospective" reports.	The registry will encourage prospective registration, which is defined as those exposures registered before the **end of the pregnancy (i.e., live birth, fetal loss, etc). Two definitions for prospective reports of pregnancy will be used in this registry, traditional prospective and pure prospective [Holmes, 2008; Tomson, 2004]. Traditional prospective reports will include all women who enroll in the registry before the end of pregnancy (live birth, fetal loss, etc), regardless of known normal or abnormal prenatal test results. Pure prospective reports of pregnancy will be those where the enrollee did not know at the time of enrollment, whether**	Clarification about the new definitions for reports of traditional and prospective pregnancy

Section(s)	Previous Wording	New Wording	Rationale
		the fetus had a malformation and no prenatal testing was completed prior to enrollment. Those defined as pure prospective will be included in the primary study population.	
4.6.8.2 Retrospective Reports	Retrospective reports will be defined as those in which the outcome or anticipated outcome of pregnancy is known before enrollment. All retrospective cases reported to the registry will have data collected and entered into the database using the same procedures as for prospective cases, however, these retrospective data will be summarized separately. Inclusion of retrospective reports, in which the pregnancy outcome is already known before enrollment, can be biased toward the reporting of more unusual and severe cases and are less likely to be representative of the SLE population of women exposed during pregnancy, compared to women whose pregnancy outcome is not yet known at the time of enrollment into the pregnancy registry. A woman or her HCP is more likely to notify the registry if a negative outcome is already known. Conversely, a woman or her HCP is less likely to notify the registry retrospectively if the pregnancy outcome was normal. [Holmes LB, Baldwin EJ, Smith CR, et al. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. Neurology 2008;70:2152-2158. Honein 1999]. This potential enrollment bias	Retrospective reports **of pregnancy are** those in which **the pregnancy ended (live birth, fetal loss, etc) before enrollment or at the time of first contact with the registry.** All retrospective cases reported to the registry will have data collected and entered into the database using the same procedures as prospective cases **(traditional or pure);** however, retrospective data will be summarized separately. **Reports of pregnancy in** which the pregnancy outcome **or anticipated outcome** is already known before enrollment can be biased toward the reporting of more unusual or severe cases compared to women whose pregnancy outcome is not yet known at the time of enrollment into the pregnancy registry. A woman or her HCP is more likely to notify the registry if a negative outcome is already known. Conversely, a woman or her HCP is less likely to notify the registry retrospectively if the pregnancy outcome was normal [Holmes LB, Baldwin EJ, Smith CR, et al. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. Neurology 2008;70:2152-2158. Honein 1999]. This potential enrollment bias could occur even for cases where the exposure information was obtained and documented in the medical record before the pregnancy outcome was	Clarification about the new definitions for reports of pregnancy and how these data will be analyzed

Section(s)	Previous Wording	New Wording	Rationale
	could occur even for cases where the exposure information was obtained and documented in the medical record before the pregnancy outcome was known. Therefore, retrospective cases will not be included in the primary study population, but will be evaluated to aid in detection of potential early signals and also described separately in registry reports. As with prospective reports (see Section 4.6.8.1), retrospective reports of birth defects in infants after the 1st year of life and by 6 years of age will not be included in the primary study population, but will be described in the text of the registry interim and final reports.	known. Therefore, retrospective cases **and traditional prospective cases** will not be included in the primary study population, but will be **summarized separately in interim and final reports** to aid in detection of potential early signals. The frequency of birth defects in infants after the 1st year of life and by 6 years of age will be described in the text of the registry interim and final reports stratified by traditional prospective, pure prospective and retrospective reports of pregnancy. The frequency of birth defects in infants after the 1st year of life and by 6 years of age will be described in the text of the registry interim and final reports stratified by **traditional prospective, pure prospective and retrospective reports of pregnancy.**	
4.6.8.4 Evaluable Registry Reports	Prospectively reported evaluable cases will be included in the primary study population section of the registry report. Evaluable retrospective reports will be summarized separately in the interim and final reports.	**Pure prospective** reported evaluable cases will be included in the primary study population section of the registry report. Evaluable **traditional prospective and** retrospective reports will be summarized separately in the interim and final reports.	Clarification about the new definitions for reports of pregnancy and how these data will be analyzed
4.8 Endpoints and Data Analysis	This pregnancy registry will be a prospective cohort study and descriptive statistics will be performed for all prospective, evaluable data.	This pregnancy registry will be a prospective cohort study and descriptive statistics will be calculated **separately for traditional prospective and for pure prospective** evaluable data **The registry data will be used to conduct risk estimation and comparative analyses for the primary endpoint of birth defects and descriptive analyses for all secondary endpoints (i.e. pregnancy and infant outcomes). The presence of a birth defect will be summarized**	Clarification about the new definitions for reports of pregnancy and how these data will be analyzed

Section(s)	Previous Wording	New Wording	Rationale
		for registry participants with SLE who have been exposed to commercially supplied belimumab within the four months prior to and/or during pregnancy. The birth defect prevalence will be calculated as the percentage of birth defects from the total number of live births [Parker, 2010]; this approach is commonly used in other drug exposure pregnancy registries [Covington, 2004; Tomson, 2004; Holmes, 2008]. Fetal losses occurring at or after 20 gestational weeks with reported birth defects will be included in the estimation for the risk for birth defects to increase sensitivity and to allow comparison of the registry birth defect rates with the CDC MACDP and EUROCAT surveillance systems. An analysis will also be conducted to include fetal losses with reported birth defects occurring at less than 20 gestational weeks in the calculation of risk for birth defects.	
4.8.1 Analysis Population	The primary study population for which analyses will be presented includes prospective evaluable cases in participants having SLE considered exposed to belimumab (Section 4.4) that are not lost to follow-up (i.e., cases with appropriate outcome information that meet the minimum criteria for evaluation as specified in Section 4.1). While the primary study population is prospectively reported pregnancies, which can be used to ascertain actual population rates of events, the registry will complement its analyses by comprehensive review of other sources of information about pregnancy outcomes, including	The primary study population for which analyses will be presented includes **pure** prospective evaluable cases in participants having SLE considered exposed to **commercially supplied** belimumab (Section 4.4) that are not lost to follow-up (i.e., cases with appropriate outcome information that meet the minimum criteria for evaluation as specified in Section 4.1). While the primary study population is **pure** prospective reported pregnancies, which can be used to ascertain actual population rates of events, the registry will complement its analyses by comprehensive review of other sources of	Clarification about the new definitions for reports of pregnancy and how these data will be analyzed

Section(s)	Previous Wording	New Wording	Rationale
	retrospective reports.	information about pregnancy outcomes, including **traditional prospective** and retrospective reports.	
4.8.1.2 Analysis Parameters for Birth Defects	Most structural defects originate in the first trimester of pregnancy, the period of organogenesis. Therefore, the outcome data for prospective evaluable cases will be stratified by the earliest trimester of exposure to belimumab. For this registry, gestational weeks will be estimated from the most reliable EDD as reported by the HCP. If a CEDD is provided by the HCP, it will be used instead. The date of conception will be calculated as the most reliable EDD minus 38 weeks. If the EDD is not available or never estimated, the first day of the LMP may be used to estimate gestational age. The second trimester begins at week 14 after the date of conception or LMP, and the third trimester begins at week 28. Only cases meeting the CDC MACDP criteria for a defect or with 2 or more conditional defects will be included in the primary study population. Single minor defects do not constitute a birth defect according to the CDC MACDP classification; therefore, they will be listed in the report, but not included in the primary study population.	Most structural defects originate in the first trimester of pregnancy, the period of organogenesis. Therefore, the outcome data for **pure** prospective evaluable cases will be stratified by the earliest trimester of exposure to belimumab. For this registry, gestational weeks will be estimated from the most reliable EDD as reported by the HCP. If a CEDD is provided by the HCP, it will be used instead. The date of conception will be calculated as the most reliable EDD minus 38 weeks. If the EDD is not available or never estimated, the first day of the LMP may be used to estimate gestational age. The second trimester begins at week 14 after the date of conception or LMP, and the third trimester begins at week 28. Only cases meeting the CDC MACDP criteria for a defect or with 2 or more conditional defects will be included in the primary study population. Single minor defects do not constitute a birth defect according to the CDC MACDP classification; therefore, they will be listed in the report, but not included in the primary study population. **The birth defect primary analysis will include pure prospective pregnancies and a sensitivity analysis with traditional prospective pregnancies is planned.**	Clarification about the new definitions for reports of pregnancy and how these data will be analyzed

Section(s)	Previous Wording	New Wording	Rationale
5 Sample Size and Power/Precision Calculations	This registry will be descriptive and will seek to enroll approximately 500 commercially supplied belimumab-exposed prospective pregnancies.	This registry will be descriptive and will seek to enroll approximately 500 **traditional** prospective pregnancies **exposed to commercially supplied belimumab**.	Clarification about the type of prospective pregnancy for target enrollment
6 Study Limitations	Because early prenatal testing is so prevalent, it may be difficult to achieve adequate numbers of prospectively identified participants if all pregnancies with prior prenatal testing are excluded from the analysis. Therefore, the primary study population will include pregnancies enrolled prior to outcome but after prenatal test as long as the test does not indicate an abnormality. However, this practice could potentially bias the results by lowering the overall risk of birth defects [Honein, 1999]. We will conduct analyses with and without participants who had prior prenatal testing separately, in an attempt to address potential bias. While the primary analysis population in this registry will be limited to prospective reports, some pregnancy exposures will be reported only following pregnancy outcome (retrospective cases). In general, retrospective reports of exposures to therapy following notification of outcome are biased toward reporting of the severe and unusual cases and are not reflective of the general experience with the medication. Moreover, information about the total number of exposed persons is not known. Therefore, rates of outcomes cannot be calculated from these data. However, a series of reported birth defects can be evaluated to detect patterns of specific birth defects and can assist with identification of	The primary study population will include **pure** prospective pregnancies **(i.e. (a) enrollee did not know at the time of enrollment whether the fetus had a malformation and (b) no prenatal testing was completed prior to enrollment). Sensitivity analyses will be conducted with traditional prospective pregnancies comprised of women who enroll in the registry prior to the end of pregnancy (live birth, fetal loss, etc), regardless of known normal or abnormal prenatal test results.** While the primary analysis population in this registry will be limited to **pure** prospective reports, some belimumab-exposed pregnancies will be reported after **the pregnancy ended (i.e. live birth, fetal loss, etc or retrospective report) or following notification of an abnormal prenatal test result.** In general, **reports made to the registry after the pregnancy has ended and/or notification of an abnormal prenatal test result** are biased toward reporting of the severe and unusual cases and are not reflective of the general experience with the medication. Moreover, information about the total number of exposed persons is not known. Therefore, rates of outcomes cannot be calculated from these data. However, a series of reported birth defects can be evaluated to detect patterns of specific birth defects and can assist with identification of	Clarification about study limitations

Section(s)	Previous Wording	New Wording	Rationale
	potential early signals of therapy risks. As reporting of pregnancies will be totally voluntary, it is possible that even in prospectively reported cases, potential bias could exist. For example, high-risk pregnancies or low-risk pregnancies may be more likely to be reported.	potential early signals of therapy risks. As reporting of pregnancies will be totally voluntary, it is possible that even in **pure** prospective reported cases, potential bias could exist. For example, high-risk pregnancies or low-risk pregnancies may be more likely to be reported.	
7.2 Informed Consent	Belimumab is not approved for treatment of minors and the registry will not proactively seek to recruit minors who are pregnant and who have been exposed to belimumab within 4 months prior to and/or during pregnancy.	Belimumab is not approved for treatment of minors.	EMA request to remove text after minors
7.9 Registry Coordinating Center	• Ensuring that all case reports of adverse events, including adverse pregnancy outcomes, which are considered by the HCP to have a reasonable possibility of attribution to belimumab, are forwarded to GSK/HGS drug safety within 1 business day of registry notification for regulatory reporting requirements. • Ensuring that all follow-up data on adverse events which are considered to have a reasonable possibility of attribution to belimumab and that is attainable from HCPs is forwarded to GSK/HGS drug safety within 1 business day of receipt and entered into the registry database	• Ensuring that all case reports of **serious** adverse **events and all adverse pregnancy outcomes** are forwarded to **GSK** within 1 business day of registry notification for regulatory reporting requirements **and entered into the registry database** • Ensuring that all follow-up data **that are attainable from HCPs on serious** adverse events **and all adverse pregnancy outcomes are** forwarded to **GSK Safety Department** within 1 business day of receipt and entered into the registry database	Clarification to align with Section 7.4 that was revised during protocol amendment01

10.5. Appendix 5: Protocol Amendment 03 Changes

Protocol Amendment 03 applies to all countries and sites.

Protocol GlaxoSmithKline Document Number 2010N108011_02 was amended. Detailed descriptions of substantive changes to the protocol are listed below. Additional administrative and minor typographical/editorial changes have also been made

Section(s)	Previous Wording	New Wording	Rationale
Protocol summary: objective; Section 2.1	To evaluate pregnancy and infant outcomes for pregnancies in women with SLE exposed to commercially supplied belimumab within the 4 months prior to and/or during pregnancy.	The **main objective** is to evaluate pregnancy and infant outcomes for pregnancies in women with SLE exposed to commercially supplied belimumab within the 4 months prior to and/or during pregnancy. **In addition, pregnancy and infant outcomes will also be collected for pregnancies in women with SLE from the SABLE (Safety and Effectiveness of Belimumab in Systemic Lupus Erythematosus) protocol who are not exposed to belimumab.**	To clarify the updated objective of the Registry to additionally allow inclusion of unexposed patients in the SABLE protocol to be enrolled into the Benlysta Pregnancy registry as per EMA request.
Protocol summary: study population; Section 4.1	Pregnant women who have been exposed to commercially supplied belimumab within the 4 months prior to and/or during pregnancy will be eligible to participate in the registry. Minimum criteria for enrollment will be the following: Sufficient evidence to confirm that exposure to commercially supplied belimumab occurred within the 4 months prior to and / or during pregnancy	Minimum criteria for enrolment will be the following: • Exposure criteria: • **<u>For belimumab exposed pregnant women;</u>** Sufficient evidence to confirm that exposure to commercially supplied belimumab occurred within the 4 months prior to and / or during pregnancy (“belimumab exposed”)	Clarification of exposure criteria for both belimumab exposed participants and belimumab unexposed participants.

Section(s)	Previous Wording	New Wording	Rationale
		Or • **For belimumab unexposed pregnant women:** **Any women who became pregnant during the SABLE protocol and was not exposed to belimumab:** **Sufficient evidence to confirm that exposure to belimumab did not occur within 4 months prior to and / or during pregnancy ("unexposed")**	
Protocol summary: comparison data; Section 4.8.2	Data obtained may be compared with external data sources including information obtained from the literature.....and appropriate.	**The registry includes unexposed participants from the SABLE protocol, however, as the likely number of these participants will be small, formal comparisons of primary and secondary outcomes between belimumab exposed and unexposed participants will not be conducted.** Data obtained may be compared with external data sources including information obtained from the literature.....and appropriate.	Clarification that there will be no formal comparison of primary and secondary outcomes between belimumab exposed and unexposed participants in the Registry.
Protocol summary: number of participants	The registry will seek to enroll approximately 500 traditional prospective pregnancies exposed to commercially supplied belimumab. Research indicates that approximately…… live births.	The registry will seek to enroll approximately 500 traditional prospective pregnancies exposed to commercially supplied belimumab. Research indicates that approximately…… live births. **Furthermore, the registry will enroll as many unexposed participants as possible from the SABLE protocol.**	Clarification on number of subjects expected from SABLE protocol.

Section(s)	Previous Wording	New Wording	Rationale
Protocol summary; statistical/analytic methods	Descriptive statistics will be calculated separately for traditional prospective and for pure prospective evaluable data. The summary statistics..... Frequencies and proportions of adverse pregnancy outcomes, birth defects, serious and/or clinically significant infections in infants will be calculated with corresponding 95% confidence intervals. For the primary endpoint.....confidence intervals.	Descriptive statistics will be calculated separately for traditional prospective and for pure prospective evaluable data **for belimumab-exposed subjects**. The summary statistics ..... Frequencies and proportions of adverse pregnancy outcomes, birth defects, serious and/or clinically significant infections in infants will be calculated with corresponding 95% confidence intervals **for both the exposed and unexposed groups.** For the primary endpoint.....confidence intervals.	Clarification of analyses for both belimumab exposed and unexposed groups.
Section 1.1	This registry is being conducted to evaluate pregnancy and infant outcomes for pregnancies in women with SLE exposed to commercially supplied belimumab within the 4 months prior to and/or during pregnancy.	Text remove to reflect updated objective (see Section 2.1) and rationale (see Section 1.2)	Clarification on updated rationale and objective for the Registry.
Section 1.2	This global Belimumab Pregnancy Registry will collect prospective data on pregnancies and pregnancy outcomes on a voluntary basis in women with SLE who have received commercially supplied belimumab within the 4 months prior to and/or during pregnancy. The registry will also evaluate outcomes of infants born to mothers who were exposed to commercially supplied belimumab within the 4	This global Belimumab Pregnancy Registry will collect prospective data on pregnancies and pregnancy outcomes on a voluntary basis in women with SLE who have received commercially supplied belimumab within the 4 months prior to and/or during pregnancy **("exposed" patients) and in those women with SLE that have not received belimumab within the 4 months prior to and/or during pregnancy ("unexposed" patients) from the Safety and Effectiveness of Belimumab in Systemic Lupus Erythematosus (SABLE) protocol. The unexposed patient group was added to this registry at the request of the European Medicines Agency (EMA).** The registry will also evaluate outcomes of infants born to **both exposed and unexposed mothers**.	Clarification of updated rationale of the Registry to collect data for both belimumab exposed and unexposed participants.

Section(s)	Previous Wording	New Wording	Rationale
	months prior to and/or during pregnancy. This registry.....with SLE. GSK will sponsor the Belimumab Pregnancy Registry in countries where it holds Marketing Authorization.	This registry..... with SLE. GSK will sponsor the Belimumab Pregnancy Registry in countries where it holds Marketing Authorization **and where belimumab is available by prescription.**	Clarification on where the study will be conducted, given that belimumab is not commercially available in all countries where market authorization has been granted.
Section 3	Registry interim data reports will be produced at least annually and a final data report will be produced at the conclusion of the registry. Reports will be submitted to regulatory authorities as applicable and made available to HCPs. Data may also be reported at scientific conferences or published in scientific journals.	Registry interim data reports will be produced at least annually and a final data report will be produced at the conclusion of the registry. **Interim and final reports will be made available to HCPs and the final report will be submitted to regulatory authorities**. Data may also be reported at scientific conferences or published in scientific journals. **In addition, GSK central safety department (CSD) will produce periodic benefit risk evaluation reports (PBRER) for submission to regulatory authorities.**	Clarification on target audience for both interim and final reports and addition of text indicating inclusion of Registry data in PBRER submission for regulatory authorities.
Section 4.3.1	Small for gestational age (SGA): defined as an infant whose birth weight, length, or head circumference is less than the 10th percentile for the gestational age. It is based on data derived from an appropriate reference population. The registry will utilize the sex specific international growth reference currently recommended by the World Health Organization (WHO) (de Onis, 1996; Williams, 1982).	Small for gestational age (SGA): defined as an infant whose **birth weight** is less than the 10th percentile for the gestational age. It is based on data derived from an appropriate reference standards from the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) for those born at ≥33 weeks gestational age (Villar, 2014). The INTERGROWTH-21st standards are the latest available global reference standards, representing contemporary information from an international, multiethnic, diverse population and have been specifically developed for modern research. As the	Clarification that SGA will be based solely on birthweight as weight data is likely to be collected more reliably and consistently than length or head circumference between sites; Alexander (1996) does not include length or head circumference in the definition. The reference standards utilised have been updated to Villar 2014 and Alexander 1996 to represent more contemporaneous population information. References de Onis, 1996; Williams, 1982 have

Section(s)	Previous Wording	New Wording	Rationale
		INTERGROWTH-21st standards are valid for infants born between $33^{0/7}$ and $42^{6/7}$ weeks gestation, SGA will be additionally classified using the reference standard endorsed by American Congress of Obstetricians and Gynecologists (ACOG) which is applicable for the entire range of gestational age (Alexander, 1996).	been removed from the reference list.
Section 4.4	One complete or partial dose of commercially supplied belimumab, administered within the 4 months (i.e., a period of approximately 5 belimumab terminal half-lives) prior to and /or during pregnancy, will constitute exposure. Belimumab exposure will be further categorized by earliest trimester of exposure, as described in Section 4.8.1.2	**For belimumab-exposed subjects:** One complete or partial dose of commercially supplied belimumab, administered within the 4 months (i.e., a period of approximately 5 belimumab terminal half-lives) prior to and /or during pregnancy, will constitute exposure. Belimumab exposure will be further categorized by earliest trimester of exposure, as described in Section **4.8.2.2.** **For belimumab "unexposed" subjects: Treatment with any immunosuppressants (azathioprine, methotrexate, cyclophosphamide, mycophenolate, biologics or others) as defined in the SABLE protocol as SLE treatment, excluding belimumab (Protocol HGS1006-C1124). There must be sufficient evidence to confirm that exposure to belimumab did not occur within 4 months prior to and / or during pregnancy for a woman to be classified within this group.**	Clarification of exposure definition for the belimumab exposed and unexposed groups.
Section 4.6	Women who received commercially supplied belimumab within the 4 months prior to and /or during pregnancy will be eligible to voluntarily enroll in this prospective cohort study. The registry awareness program will encourage enrollment as early in pregnancy as	**This is a voluntary registry** and the registry awareness program will encourage enrollment as early in pregnancy as possible, so as to minimize bias. **In addition, all investigators from the SABLE protocol will be made aware of the Registry and will inform eligible women of their**	Clarification that the registry is open to both belimumab exposed participants and belimumab unexposed participants from the SABLE protocol

<table>
<tr><th>Section(s)</th><th>Previous Wording</th><th>New Wording</th><th>Rationale</th></tr>
<tr><td></td><td>possible, so as to minimize bias.

• Belimumab exposures, medications, and concurrent medical conditions .....the pregnancy.</td><td>option to co-participate in this Registry.

• Belimumab exposures, other SLE treatment, other medications and concurrent medical conditions ..... the pregnancy.</td><td>Clarification that data on other SLE treatments will also be captured to allow exposure status of the non-belimumab exposed participants to be defined.</td></tr>
<tr><td>Section 4.6.1
(Table 4-1)</td><td>Table 4-1<table><tr><th>Information Requested</th><th>Data source</th></tr><tr><td>Maternal disease severity</td><td>Belimumab Prescriber</td></tr><tr><td>Belimumab exposure information</td><td>Belimumab Prescriber</td></tr><tr><td>Concurrent conditions</td><td>Belimumab Prescriber & Obstetric HCP</td></tr><tr><td></td><td></td></tr><tr><td>History of serious or clinically/significant infections</td><td>Obstetric & Pediatric HCP</td></tr><tr><td>Lactation status</td><td>Obstetric HCP</td></tr><tr><td>Breastfeeding status</td><td>Obstetric and/or Pediatric HCP</td></tr></table></td><td>Table 1<table><tr><th>Information Requested</th><th>Data source</th></tr><tr><td>Maternal disease severity</td><td>SLE Prescriber</td></tr><tr><td>Belimumab exposure information</td><td>SLE Prescriber</td></tr><tr><td>Concurrent conditions</td><td>SLE Prescriber and/or Obstetric HCP</td></tr><tr><td></td><td></td></tr><tr><td>History of serious or clinically/significant infections</td><td>Obstetric and/or Pediatric HCP</td></tr><tr><td></td><td></td></tr><tr><td>Breastfeeding status</td><td>Obstetric and/or Pediatric HCP</td></tr></table></td><td>Clarification of table numbering (referred to in Section 4.6)

For belimumab provider to SLE provider: clarification that data on all SLE treatments will be collected.

For concurrent conditions, infections and breastfeeding status, clarification that data may be collected from either stated data source and not both.

Clarification that lactation status has been removed as registry captures information on administration of belimumab post -partum during breastfeeding (referring to the infant) only (where breastfeeding is defined as provision of mother’s own milk for infant nutrition-see Glossary).</td></tr>
<tr><td>Section 4.6.2;
Section 4.6.3.1;
Section 4.6.3.2</td><td>Maternal Belimumab Exposure and Other Exposures

• Belimumab treatment course, including</td><td>Maternal Belimumab or other SLE treatment Exposure and Other Exposures

• Belimumab or other SLE treatment</td><td>Clarification that exposure information is captured for belimumab unexposed group.</td></tr>
</table>

Section(s)	Previous Wording	New Wording	Rationale
	doses received, route and dates of treatment	**course** with dates of treatment. **Dose and route of administration will be captured for belimumab exposed participants only.**	
Section 4.6.3	Around the end of the second trimester and after pregnancy outcome, the *Obstetrical Follow-up Form* and *Obstetrical Pregnancy Outcome Form* (respectively) will be requested from the HCP. *Belimumab Prescriber* data collection forms will also be requested from the HCP at these time points.	Around the end of the second trimester and after pregnancy outcome, the *Obstetrical Follow-up Form, Obstetrical Pregnancy Outcome Form* (respectively) and ***Pediatric Outcome Form*** will be requested from the HCP. ***SLE treatment Prescriber*** data collection forms will also be requested from the HCP at these time points.	Clarification of data sources for data collection.
Section 4.6.4	Infant follow-up case report forms will be requested from the pediatric HCP for live-born infants at approximately 4 and 12 months of age: • Date of assessment • ..... • Breastfeeding status • Lactation status • Mother's belimumab exposure post-partum, if dosed during lactation	***Pediatric Follow-up forms*** will be requested from the pediatric HCP for live-born infants at approximately 4 and 12 months of age: • Date of assessment • ..... • Breastfeeding status TEXT REMOVED • Mother's belimumab **or other SLE treatment exposure post-partum, if dosed while breastfeeding**	Clarification of data collection form used to collect data. Clarification that lactation status has been removed (see Section 4.6.1). Clarification that exposure to belimumab and other SLE treatments will be captured in the post-partum period.
4.6.8.1	Prospective infant follow-up beyond the first year of life will not be solicited by the registry. However, while the study remains active, ... registry reports. Prospective reports of birth defects in infants beyond the first year of life and by 6 years of age will not be included in the primary study	Prospective infant follow-up beyond the first year of life will not be **routinely solicited by the registry but follow-up may be extended on a case-by-case basis if deemed medically necessary.** In addition, ... registry reports. Prospective reports of birth defects in infants beyond the first year of life and by 6 years of age will not be included in the primary study	Clarification that additional follow-up after one year will be allowed in order to meet medical needs. Clarification of that these analyses will only be provided in the final report for the Registry.

Section(s)	Previous Wording	New Wording	Rationale
	population, but will be described in the text of the registry interim and final reports.	population, but will be described in the text of the registry **final report.**	
4.6.8.2	The frequency of birth defects in infants after the 1st year of life and by 6 years of age will be described in the text of the registry interim and final reports stratified by traditional prospective, pure prospective and retrospective reports of pregnancy.	The frequency of birth defects in infants after the 1stYear of life and by 6 years of age will be described in the text of the registry **final report** stratified by traditional prospective, pure prospective and retrospective reports of pregnancy.	Clarification of that these analyses will only be provided in the final report for the Registry (see 4.6.8.1 above).
4.6.8.4	Evaluable traditional prospective and retrospective cases will be summarized separately in the interim and final reports. Participant-reported data without HCP confirmation will also be summarized separately in the interim report.	Evaluable **belimumab exposed** traditional prospective and retrospective cases **as well as unexposed cases** will be summarized separately in the interim and final reports. Participant-reported data without HCP confirmation will also be summarized separately in the **final report.**	Clarification that both belimumab exposed and unexposed evaluable cases will be included in interim and final reports; and data without HCP confirmation will only be included in the final report.
4.8	This pregnancy registry will be a prospective cohort study and descriptive statistics will be calculated separately for traditional prospective and for pure prospective evaluable data.	This pregnancy registry will be a prospective cohort study and descriptive statistics will be calculated separately for traditional prospective and for pure prospective evaluable data for **belimumab exposed participants. Data for belimumab exposed participants will be summarized separately from unexposed patients**.	Clarification of analysis populations for the Registry.
4.8	Section starting: The summary statistics ..... confidence intervals.	**Section 4.8.1 Belimumab exposed participants (section header added)** No substantive changes to the text	Section number has been added to clarify that these analyses apply to belimumab exposed participants only.
Section 4.8.1	4.8.1 Analysis Population	4.8.2 **Belimumab** Analysis Population	Clarification that these analyses apply to belimumab exposed participants only (Section number

Section(s)	Previous Wording	New Wording	Rationale
			inserted).
Section 4.8.1.1	4.8.1.1 Exclusions for Analysis Purposes Invalid cases (Section 4.6.8.5), pregnancies deemed lost to follow-up, retrospective cases and cases where participants do not have SLE, will be excluded from the primary study population	4.8.2.1 Exclusions for Analysis Purposes Invalid cases (Section 4.6.8.5), pregnancies deemed lost to follow-up, retrospective cases, cases where participants do not have SLE**, and SLE patients not exposed to belimumab** will be excluded from the primary **belimumab study** population.	Clarification of the primary analyses population.
Section 4.8.1.2	4.8.2.1 Analysis Parameters for Birth Defects	4.8.2.2 Analysis Parameters for Birth Defects	Clarification of section numbering (no change to section text).
Section 4.8.1.3	4.8.1.3 Sequential Pregnancies The number .....Section 4.8.1.1.	**4.8.2.3** Sequential Pregnancies The number ..... **Section 4.8.2.1.**	Clarification of section numbering and cross referencing.
Section 4.8.1.4	4.8.1.4 Multiple Gestation pregnancies The number, ...Section 4.8.1.1.	**4.8.2.4** Multiple Gestation pregnancies The number, ... **Section 4.8.2.1.**	Clarification of section numbering and cross referencing.
Section 4.8.2	4.8.2 Comparison groups Given the inherent difficulties in identifying a single optimal comparison cohort, several different cohorts may be used to provide background data for potential safety signal generation in the pregnancy registry. This section ..... be implemented.	**4.8.3** Comparison groups **The registry includes unexposed participants from the SABLE protocol, however, as the likely number of these participants will be small, formal comparisons of primary and secondary outcomes between belimumab exposed and unexposed participants will not be conducted.** Given the inherent difficulties in identifying a single optimal comparison cohort, several different	Clarification of section number and analyses of the unexposed group.

Section(s)	Previous Wording	New Wording	Rationale
		cohorts may be used to provide background data for **interpretation of data from the belimumab exposed participants** in the pregnancy registry. This section ..... be implemented.	
Section 4.8.2.1	4.8.2.1 Population-Based Birth Defects Surveillance Programs	**4.8.3.1** Population-Based Birth Defects Surveillance Programs	Clarification of section numbering (no change to section text).
Section 4.8.2.2	4.8.2.2 External Data Sources	**4.8.3.2** External Data Sources	Clarification of section numbering (no change to section text).
Section 4.8.2.3	4.8.2.3 Qualitative Case Analysis	**4.8.3.3 Qualitative Case Analysis**	Clarification of section numbering (no change to section text).
Section 4.8.3	4.8.3 Essential Analysis A confidence interval estimation approach will be employed to descriptively compare the outcomes observed in the pregnancy registry to external data.	**4.8.4** Essential Analysis **of belimumab-exposed participants** A confidence interval estimation approach will be employed to descriptively compare the outcomes observed in the **belimumab exposed participants of the** pregnancy registry to external data.	Clarification of section numbering and of the analysis population (no change to section text).
Section 4.8.3.1	4.8.3.1 Adverse Pregnancy Outcomes	**4.8.4.1** Adverse Pregnancy Outcomes	Clarification of section numbering (no change to section text).
Section 4.8.3.2	4.8.3.2 Birth Defects	**4.8.4.2** Birth Defects	Clarification of section numbering (no change to section text).
Section 4.8.3.3	4.8.3.3 Serious and/or Clinically significant Infections in Infants	**4.8.4.3** Serious and/or Clinically significant Infections in Infants	Clarification of section numbering (no change to section text).
Section 4.8.3.4	4.8.3.4 Demographics and Baseline	**4.8.4.4** Demographics and Baseline Characteristics	Clarification of section numbering

Section(s)	Previous Wording	New Wording	Rationale
	Characteristics		(no change to section text).
(Section 4.8.5)	No previous section 4.8.5	**4.8.5 Analyses for the unexposed group**	Clarification of analyses for the unexposed group (new section inserted).
Section 4.8.4	4.8.4 Data Handling Conventions	**4.8.6** Data Handling Conventions	Clarification of section numbering (no change to section text).
Section 6	The primary study population will include pure prospective pregnancies,	The primary study population of **belimumab exposed participants** will include pure prospective pregnancies	Clarification of analyses population.
Section 7.4	Serious adverse events (SAEs) will be defined as those adverse events that result in death,..... reporting purposes). If an AE.....registry notification. GSK will then ..... the infants. The registry interim report may be appended to submissions to regulatory authorities where required. The interim report, which is planned to be published at least annually, will contain the background, study design, and the analysis plan. It will summarize the study status and the cumulative data on the registry to date.	**For both belimumab exposed and unexposed participants**, serious adverse events (SAEs) will be defined as those adverse events that result in death, ...reporting purposes). If an AE ..... registry notification. GSK will then ..... the infants. **Paragraph removed.**	Clarification that SAE reporting will apply to both belimumab exposed and unexposed participants in the same way.
Section 7.10	Additionally, the birth defect evaluator will provide an opinion regarding the possible temporal association of the belimumab exposure to the development of observed defects.	Additionally, the birth defect evaluator will provide an opinion regarding the possible temporal association of the belimumab exposure **or other SLE treatment exposure** to the development of	Clarification that the birth defect evaluator will review all cases (exposed and unexposed) in the

Section(s)	Previous Wording	New Wording	Rationale
		observed defects.	Registry.
Section 7.11	No previous text	**The unexposed cases and those exposed to other SLE treatments will be reviewed and used in evaluating potential belimumab signals.**	Clarification that the birth defect evaluator will review all cases in the Registry.
Section 7.12	• Collaborating with belimumab prescribers as well as investigators who are involved in a clinical trial or post marketing SLE studies.	• Collaborating with belimumab prescribers as well as investigators who are involved in a clinical trial or post marketing SLE studies**, including the SABLE protocol.**	Clarification that SABLE investigators will act as collaborators.
Section 7.13	An interim data report will be generated at least annually, and on closure of the registry, a final report will be similarly generated. These reports will contain the background, study design, including countries where participant recruitment is occurring, and the analysis plan. The reports will summarize the study status and the cumulative data on the registry to date. Interim and final reports will be submitted to the relevant regulatory authorities. Ad hoc interim reports will be generated if indicated by agreement with the SAC. The most recent interim report of registry data will be available to HCPs on a publicly accessible registry Web site.	An interim data report will be generated at least annually; **this will summarize the study status and the cumulative data on the registry to date including information on the primary and secondary endpoints. At the planned end of the registry, a final report will be generated. The comprehensive, RAP-specified final** report will contain the background, study design, including countries where participant recruitment is occurring, and the **full** analysis plan. **PBRER** and the final registry report will be submitted to the relevant regulatory authorities and the most recent interim report of registry data will be available to HCPs on a publicly accessible registry Web site. **Ad hoc data summaries will be generated if indicated by agreement with the SAC.**	Clarification of the study reporting formats.

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10.6. Appendix 6: Protocol Amendment 04 Changes

Protocol Amendment 04 applies to all countries and sites.

Protocol GlaxoSmithKline Document Number 2010N108011_03 was amended. Detailed description of changes to the protocol are listed below. Additional administrative and minor typographical/editorial changes have also been made.

Section(s)	Previous Wording	New Wording	Rationale
Updates to Sponsor Information Page	GlaxoSmithKline 1-3 Iron Bridge Road Stockley Park West Uxbridge, Middlesex UB11 1BT, UK Telephone: PPD	GlaxoSmithKline **980 Great West** Road **Brentford** Middlesex **TW8 9GS** UK Telephone: PPD	Site closer resulting in change of Sponsor address
Updates to section 4.6.8.3	For a prospective report or pregnancy where follow-up information on the pregnancy outcome is never obtained, unavailable, and/or where the indication of a birth defect is designated as unknown, the pregnancy will be considered lost to follow-up. Cases lost to follow-up prior to pregnancy outcome will be tallied in the registry reports but not included in the primary study population. For infants, if pediatric follow-up information is never obtained, unavailable, and/or where infant status is designated as unknown, the infant will be considered lost to follow-up. Any cases with infant outcome will be analyzed according to the length of infant follow up.	For a prospective report or pregnancy where follow-up information on the pregnancy outcome, **from a HCP,** is never obtained, unavailable, and/or where the indication of a birth defect is designated as unknown, the pregnancy will be considered lost to follow-up. Cases lost to follow-up prior to pregnancy outcome will be tallied in the registry reports but not included in the primary study population. For infants, if pediatric follow-up information, **from a HCP**, is never obtained, unavailable, and/or where infant status is designated as unknown, the infant will be considered lost to follow-up. Any cases with infant outcome will be analyzed according to the length of infant follow up.	Clarification to explain that the outcome information is required from a HCP to be valid

Section(s)	Previous Wording	New Wording	Rationale
Updates to Section 7.4	An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment.	An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. **An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event), and adverse events associated with circumstances of Overdose whether accidental or intentional, Medication Errors, Abuse or effects of drug withdrawal, or Misuse.**	New wording added to include lack of efficacy text