In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

Division: Worldwide Development
Information Type: Clinical Study Report
Control: placebo and other

Title:	Meta-Analysis Results Report for Study Number 201182, GSK1550188, SLE, Pregnancy Analysis

Additional Study Design Information: Aggregate analysis of pregnancies reported in belimumab clinical trials

Phase: II – IV pooled

Compound Number: GSK1550188

Effective Date: 16-NOV-2015

Subject: Systemic Lupus Erythematosus, Pregnancy, Pregnancy Outcomes, Congenital Anomaly, birth defect

Author(s): [redacted]

Indication Studied:

Systemic Lupus Erythematosus and Pregnancy

Initiation Date: 29-MAY-2015

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Earlier CSRs NA

[redacted]
GSK, Director, Global Clinical Safety and Pharmacovigilance

Date

16 November 2015

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents. This study complies with US 21 CFR 312.120.

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ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse Event
BPR	Belimumab Pregnancy Registry
CA	Congenital Anomaly
CDC	Centers for Disease Control and Prevention
CEDD	Corrected estimated date of delivery
CFR	Code of Federal Regulations
CI	Confidence Interval
CMG	Case Management Group
CTD	Common Technical Document
eCRF	Electronic Case Report Form
EDD	Estimated Date of Delivery
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
ICH	International Conference on Harmonisation
IV	Intravenous
LMP	Last Menstrual Period
LTF	Lost to follow-up
MedDRA	Medical Dictionary for Regulatory Activities
PGA	Physician Global Assessment
SA	Spontaneous Abortion
SAE	Serious Adverse Event
SGA	Small for gestational age
SLE	Systemic Lupus Erythematosus
SOP	Standard Operating Procedure
TLF	Table, listing, figure
VEO	Value Evidence Outcomes
WHO	World Health Organization

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ETHICS AND GOOD CLINICAL PRACTICE

Each study protocol, any amendments, the informed consent, and other information that required pre-approval used in the pooled analysis were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable country-specific requirements, including US 21 Code of Federal Regulations (CFR) 312.3(b) for constitution of independent ethics committees. Ethics committee or institutional review board approvals for the studies contributing data to this aggregate analysis are maintained in the Sponsor's study file.

Each study was conducted in accordance with ICH GCP and all applicable subject privacy requirements, and, the ethical principles that are outlined in the Declaration of Helsinki for each clinical study included in the aggregate analysis see Section 9. Each study was monitored in accordance with ICH E6, Section 5.18.

In each study, investigators were trained to conduct the study in accordance with GCPs and the study protocol as defined in ICH E3, Section 9.6. Written commitments were obtained from investigators to comply with GCP and to conduct the study in accordance with the protocol.

For each study contributing subjects in this aggregate analysis, written informed consent was obtained from each subject prior to the performance of any study-specific procedures. The investigator agreed to provide the subject as much time as necessary to review the document, to inquire about details of the trial, and to decide whether or not to participate in the study. The informed consent was signed and dated by the study subject and by the person who conducted the informed consent discussion. Case report forms (CRFs) were provided for each subject's data to be recorded.

1. INTRODUCTION

Systemic Lupus Erythematosis (SLE) is a chronic and progressive autoimmune disease typically requiring lifelong treatment. More individuals with SLE 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]. SLE is associated with significant maternal and foetal morbidity, including spontaneous abortion, preeclampsia, intrauterine growth restriction, foetal death, and pre-term delivery (Molad, Borkowski et al., 2005). The frequency of foetal loss (the sum of spontaneous abortions and stillbirths) ranges from 4% to 43% (mean 19.5% ± SEM 1.6%) (Yan Yuen, Krizova et al., 2008). Yan Yuen et.al. also report that several factors may predict foetal death such as lupus disease activity, active lupus nephritis, and the presence of anti-phospholipid antibodies. Foetal prognosis depends largely on disease activity, with foetal loss ranging from 25-52% in patients with active SLE compared to 8-12% in patients with inactive SLE at the onset of pregnancy. A history of nephritis, maternal hypertension (OR 6.4), proteinuria > 0.5 g/day (OR 13.3), and the presence of anti-phospholipid antibodies (OR 17.8) have been shown to be predicative of adverse foetal outcomes. Anti-phospholipid antibodies are present in 36.8% ± SEM 6.1% of SLE patients, and are associated with foetal losses in as many as 30-83% of pregnancies.

SLE is also associated with increased risk of congenital anomalies. Using the Nova Scotia Atlee Perinatal Database, Nili et.al.(Nili, McLeod et al., 2013) compared maternal and neonatal outcomes in pregnancies complicated by clinically diagnosed SLE with those of the remaining Nova Scotia population without the clinical diagnosis of SLE delivered between 1988 and 2008. This showed that 7.1% (7/97) of the SLE pregnancy outcomes had a congenital anomaly compared to 3.6% (7640/211,355) of the non SLE control group. This correlates with a relative risk of 2.1 (0.95-4.4) and a p-value of 0.06. In a study retrospectively analyzing data from 111 pregnancies in 105 SLE patients from January 1990 to December 2008 in Peking Union Medical College Hospital in Beijing, Liu et.al.(Liu, Zhao et al., 2012) found reports of five fetal malformations (6.0%). These included three fetal heart malformations (one complete heart block, one tetralogy of Fallot, one atrial septal defect) and two multiple fetal malformations. Only one had an identifiable exposure to cyclophosphamide just prior to conception. In a large population-based study using the Canadian Offspring of SLE Mothers Registry (OSLER), 509 women with SLE had 719 children and 5824 matched controls had 8493 children. In comparison with controls, children born to women with SLE experienced more congenital heart defects (5.2% [95% CI, 3.7-7.1]) versus 1.9% [95% CI, 1.6-2.2] (Vinet, Pineau et al., 2015). There is a well-recognized association between maternal anti-Ro/SSA and anti-La/SSB antibodies and congenital heart block (Lee, Bias et al. 1983, Watson, Lane et al., 1984). More recently, Vinet et al., reported diagnoses of congenital heart defects (CHD) are 3-times more likely (OR = 2.62; 95% CI: 1.77, 3.88) among infants born to women with SLE (5%) compared with the general population (2%); this increased risk has been observed for all types of CHDs.

Current standard treatment of SLE in pregnancy is hydroxychloroquine plus the lowest dose of corticosteroid possible. Some SLE treatments are teratogenic (i.e., methotrexate),

have an association with a negative effect on pregnancy (i.e., prednisone), or have too little experience with exposure during pregnancy to understand the risks (biologics). There are risks to the mother and foetus with inadequate management of SLE disease activity as well as with medication exposures used to minimize disease activity. Where the balance lies with many of the currently available treatments is unclear.

Belimumab is a human immunoglobulin-Gγ monoclonal antibody that inhibits the biologic activity of soluble B-lymphocyte stimulator [BLyS]. In the BLISS clinical trials, subjects with autoantibody-positive SLE were randomized to treatment with placebo or belimumab 1mg/kg or 10mg/kg, while also receiving standard SLE therapy. The SLE Responder Index (SRI) response rate at week 52 was significantly improved in patients treated with belimumab compared with placebo [Navarra, 2009].

There are no adequate, well-controlled studies of the use of belimumab in pregnant women or published data reporting pregnancy outcomes for women with SLE who were exposed to belimumab in the preconception period or during pregnancy. It is known that belimumab crosses the placenta in pregnant monkeys in concentrations that result in reversible pharmacologic activity in fetuses and newborn monkeys. Overall human IgG is known to cross the placental barrier and belimumab may cause a reduction in the number of fetal B cells. Secreted concentrations into breast milk were low in two female adult monkeys [Auyeung-Kim, 2009].

Belimumab has an FDA class C pregnancy category. Human pregnancy data is available from GSK SLE phase II to III clinical trials on belimumab Powell, 2014. In these trials, women of childbearing potential with SLE were required to either be abstinent or use birth control and in the event of pregnancy, subjects were withdrawn from the study. Nonetheless, there were 83 pregnancies with known outcomes in these studies as of 14 March 2014. The long-term effects, if any, on infants exposed in to belimumab in utero are unknown. Healthcare providers and patients need belimumab pregnancy-related data to make informed decisions regarding reproductive health. In the published pregnancy outcomes to date, belimumab treatment was discontinued when the pregnancy was recognized. However, in some ongoing safety, real world clinical trials, it is no longer mandatory to discontinue belimumab treatment in pregnancy and the investigator is directed to follow the guidance in the label, leaving the decision to the discretion of the treating physician.

There is currently a belimumab pregnancy registry (BPR) enrolling subjects who become pregnant while taking commercially supplied belimumab. These pregnancy outcomes are not included in this report as the information for the pregnancy registry is published separately and updated annually with the new information. At this time, there are too few outcomes to add meaningful information to this analysis.

Purpose

To evaluate maternal, fetal and infant outcome data for subjects with systemic lupus erythematosus (SLE) who were exposed to belimumab during pregnancy

2. STUDY OBJECTIVE(S)

The primary objective was to determine if there is an increase in birth defects in infants born to women with SLE who were exposed to belimumab during pregnancy. A full listing of trials appears in Section 9 List of clinical trials included in aggregate analysis.

Secondary objectives include evaluating pregnancy outcomes including live birth, (term and preterm birth), spontaneous miscarriage, elective abortion, and still birth. Another key secondary objective of the analysis was to evaluate concomitant medication use prior to pregnancy.

3. STUDY ADMINISTRATIVE STRUCTURE

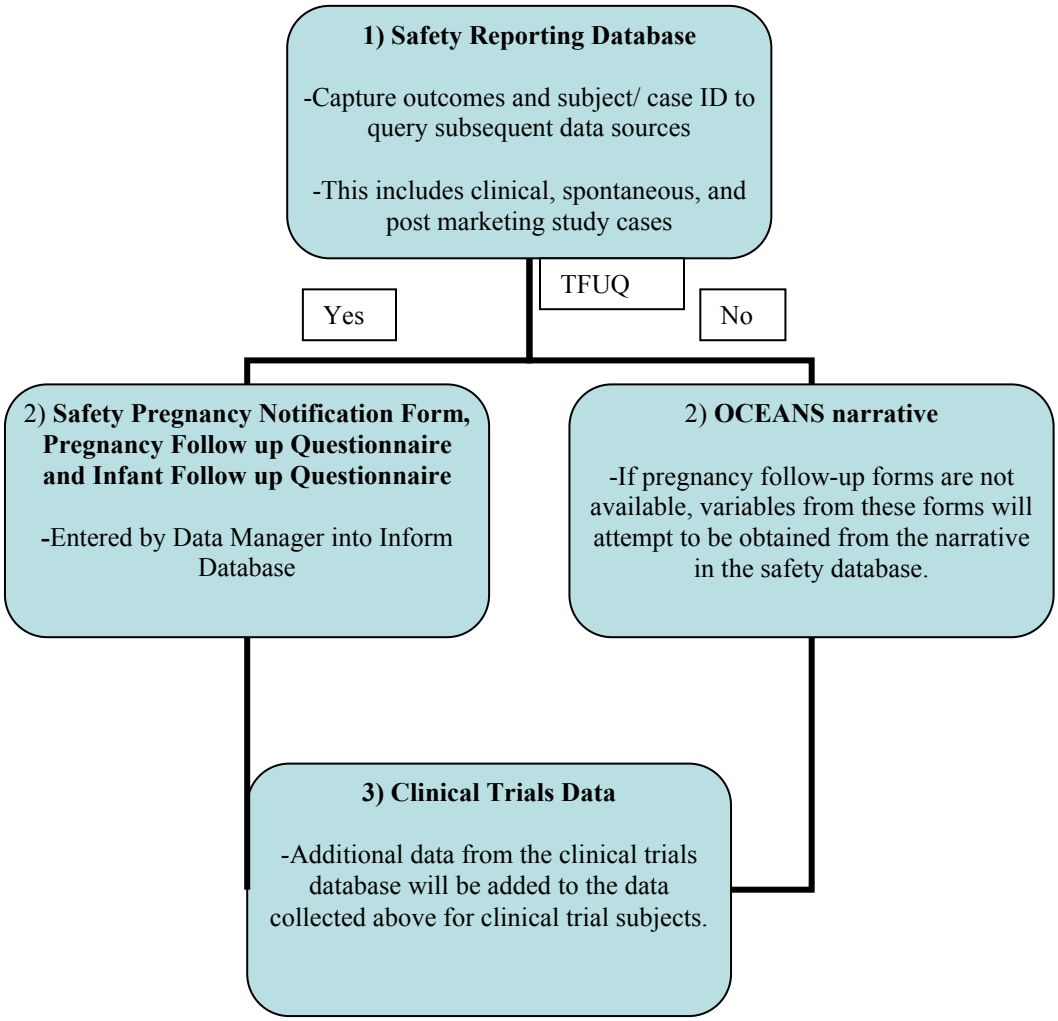
All pregnancies reported in belimumab clinical trials were identified in the GSK Safety Reporting Database. The search was based on the SMQ Pregnancy and Neonatal Topics. In addition, all cases involving a pregnant patient are included. Cases involving females over 60 years of age and adult males (where the case was not reported as a partner pregnancy) have been excluded. The primary population includes all pregnancies with an unblinded treatment assignment prior to the 08 March, 2014 data lock point reported in belimumab SLE clinical trials up to 08 March 2014... Pregnancy outcomes, estimated date of delivery, disease activity, laboratory data, and each data variable was derived from the clinical trial database and/or the GSK safety database for the purpose of evaluating maternal, fetal and infant outcome data for subjects with systemic lupus erythematosus (SLE) who were exposed to belimumab during pregnancy. Timing of exposure was calculated by adding 100 days (five elimination half-lives of belimumab) to the last belimumab dose. A full listing of clinical trials is given in Section 9.

4. INVESTIGATIONAL PLAN

4.1. Study Design

Individual clinical trial pregnancies were identified from the GSK safety reporting data base, and appropriate data was collected as outlined in Figure 1. Data for key variables were collected from the GSK Safety Database and the Clinical Trial Databases.

Figure 1 Summary of Data Sources



The data evaluated in this study included the following for each pregnant subject:

- Demographic and baseline characteristics
- Medical history at 1) baseline, 2) at the time of initial pregnancy diagnosis, and 3) ongoing during pregnancy.
- Baseline SLE History (baseline assessments
    - Physician Global Assessment (PGA) score
    - Physician Global Assessment (PGA) score
    - SLICC/ACR Damage Index (SDI) score, and
    - Laboratory parameters (autoantibody status)
- Primary Objective: Birth defects

- Secondary Objectives: Pregnancy outcome
- Subgroups **(see** Table 1**:Subgroups)**

Table 1 Subgroups

Subgroup	Definition	Outcomes
Lost to Follow-up (Pregnancy)	Participants with no pregnancy outcome or birth data	Medical History, Maternal Age at LMP, SLE History, Geographic Region
Clinical[1] and Spontaneous cases	Participants grouped by clinical pregnancy and spontaneous event (including spontaneous report and post marketing surveillance).	Primary and Secondary Endpoints
Level of Belimumab Exposure	Defined using exposure dosage proximal to pregnancy start.	Primary and Secondary Endpoints in clinical subjects only
Maternal Age	<35 years and >=35 years based on age at estimated LMP	Primary and Secondary Endpoints
Geographical Region	North America, Europe, Rest of World (Asia, South America, Mexico)	Primary and Secondary Endpoints
Disease Severity 1	PGA <2, PGA ≥ 2 before pregnancy	Primary and Secondary Endpoints
Disease Severity 2	SDI ≤1, SDI > 1 before pregnancy	Primary and Secondary Endpoints
Immunosuppressants / Concomitant Medications	Concomitant medications and potential groupings of steroids, antimalarials and immunosuppressants (i.e., Steroids only, antimalarial only, steroids + antimalarials, Steroids + antimalarials +immunosuppressants, and all of their combinations). These were reviewed by the medical monitor or healthcare professional for accuracy	Primary and Secondary Endpoints
Pregnancy Drug Category D or X	Any concomitant medication which is in categories D or X for pregnancy safety. Reviewed by medical monitor for accuracy	Primary and Secondary Endpoints

[1]Clinical and Spontaneous report will be compared to the BPR analysis, but BPR subjects will be excluded from these analyses.

All outcome data are stratified by the trimester of exposure to belimumab at 5 half- lives (100 days) after last dose. Each exposure to belimumab during the time period of interest

is captured for all subjects. The time period of interest includes the four months prior to conception through the entire pregnancy duration. These data, including dose, route, and date of treatment will be reported in a listing.

Subjects with exposure in more than one time point will be counted for each of the appropriate time points. Additionally data will be stratified by dose prior to delivery and delivery method (IV, SC). Categories for timing of belimumab exposure are as follows:

- Prior to conception
- 1st trimester
- 2nd trimester
- 3rd trimester

4.2. Discussion of Study Design

When newer medications become available, pregnancy data are limited making it difficult to weigh the benefits and risks of a medication exposure. There are risks to the mother and foetus with inadequate management of SLE disease activity as well as with medications used to minimize disease activity. Due to the underlying complexity of the indicated population, a more in depth analysis of the clinical trial pregnancies was indicated. Variables known to affect pregnancy outcomes in the population were included to better understand the influence of the many interacting factors.

4.3. Protocol Amendment(s)

None

4.4. Selection of Study Population

The SLE belimumab clinical trials enrolled adult subjects with a clinical diagnosis of SLE according to the American College of Rheumatology (ACR) criteria and a history of a positive autoantibody test. Women in belimumab SLE clinical trials (Phase II-IV) who received study drug four months prior to conception and/or during an identified pregnancy were included in these analyses.

4.4.1. Inclusion/Exclusion Criteria

A brief description of the inclusion/exclusion criteria and the dosing regimen in the contributing clinical trials is provided below:

Phase II:

LBSL02 (n=449 treated) was a randomized, multi-center, double-blind, placebo-controlled, dose-ranging 52-week study of belimumab conducted in subjects with active SLE in US and Canada. The study was designed to evaluate the safety, tolerability, and efficacy of three doses (1, 4 and 10 mg/kg) of IV administered belimumab in combination with standard of care for 48 weeks with final efficacy assessment at Week 52. An extension period was incorporated in this trial where subjects could receive

belimumab treatment for an additional 24 weeks (placebo subjects received 10 mg/kg, while subjects receiving 1 and 4 mg/kg could remain on that dose or switch to 10 mg/kg) and subsequently, subjects could optionally continue to receive treatment (10 mg/kg) in a continuation trial

Eligible subjects had a clinical diagnosis of SLE according to the ACR criteria and "active" SLE disease, defined as a SELENA SLEDAI disease activity score of at least 4 at screening and a history of measurable autoantibodies; a positive autoantibody result was not required at screening. Subjects were to be on a stable SLE treatment regimen consisting of any of the following (alone or in combination): prednisone (from 0 to 40 mg/day in combination, from 5 to 40 mg/day alone), antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate, azathioprine, leflunomide, or mycophenolate mofetil for at least 60 days prior to Day 0. Investigators could change the subject's background medication as needed throughout the study. The only treatments prohibited were cyclosporine, IV cyclophosphamide, high dose prednisone > 100 mg/day (except for flare treatment), IV immunoglobulin (IVIG), and biologics.

Study HGS1006-C1070 was a Phase 2, multicenter, randomized, open label, study designed to evaluate the safety and tolerability of repeated SC administration of 100 mg/mL belimumab (formulation 06-C) in subjects with SLE. Study C1070 also included evaluation of biomarkers, disease activity, and repeat-dose PK. The 100 mg/mL formulation was not pursued further after this study.

In addition to stable standard of care therapy, subjects were randomized to receive SC belimumab either Q2wk or 3 times a week (3x/wk), after an initial loading dose regimen. The Q2wk group received 100 mg of belimumab (1 injection) on Days 0, 7, 14, and then every 2 weeks thereafter. The 3x/wk group received 200 mg of belimumab (2 injections of 100 mg each) on Days 0, 2, and 4 and then 100 mg (1 injection) 3x/week thereafter.

Phase III

HGS1006-C1056 (N = 826 randomized; 819 treated) and **HGS1006-C1057** (N = 867 randomized; 865 treated) were two Phase 3 multi-center, double-blind, randomized, placebo-controlled trials were designed to evaluate the efficacy and safety of belimumab in subjects with SLE. Study C1056 enrolled subjects in North America, Central America, and Europe. Study C1057 enrolled subjects in Asia-Pacific, South America, and Eastern Europe. After completing these studies, subjects could optionally receive belimumab treatment in a continuation trial (HGS1006-C1066 [C1066] for US subjects, HGS1006-C1074 [C1074] for ex-US subjects).

Eligible subjects had active SLE disease, defined as a SELENA-SLEDAI score ≥ 6 and positive ANA (ANA titer ≥ 1:80) and/or anti-dsDNA (≥ 30 IU/mL) test results at screening. Subjects were on a stable standard of care SLE treatment regimen consisting of any of the following (alone or in combination): corticosteroids, antimalarials, NSAIDs, and/or immunosuppressives. Subjects were not required to be treated with each of these drugs; the choice of agent or agents was based on clinical judgment. Angiotensin pathway antihypertensive and HMG-CoA reductase inhibitor doses were also to be stable. Biologics, IVIG, IV cyclophosphamide, and plasmapheresis were prohibited.

Subjects were excluded from the study if they had ever received treatment with a B cell targeted agent, if they had received another biologic investigational agent in the previous year; or if they were currently receiving other biologic agents.

In addition to stable standard therapy, subjects were randomized to 1 of 3 treatment groups in a 1:1:1 ratio: 1 mg/kg belimumab, 10 mg/kg belimumab or placebo.

BEL113750 is an ongoing, Phase 3 multi-center, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of belimumab in subjects with SLE located in Northeast Asia. Eligible subjects must have active SLE disease, defined as a SELENA-SLEDAI score ≥ 8 and currently sero-positive for ANA or anti-dsDNA. Subjects must be on a stable standard of care SLE treatment regimen consisting of any of the following (alone or in combination): corticosteroids, antimalarials, NSAIDs, and/or immunosuppressives.

After completing this study, eligible subjects can receive belimumab treatment in a continuation trial (BEL114333) and eligible subjects from China can continue to receive belimumab in an open-label extension of the trial (BEL113750-ext).

Long Term Continuation Trials:

LBSL99 (N = 296) was a multi-center, open-label, continuation trial of belimumab in SLE subjects with a primary objective to provide continuing treatment to subjects who achieved a satisfactory response in Study LBSL02 and to evaluate the long-term safety of belimumab in subjects with SLE. Upon completion of the extension period of LBSL02, subjects who enrolled in LBSL99 received 10 mg/kg of belimumab every 4 weeks starting 4 weeks after the last dose in the LBSL02 extension period.

HGS1006-C1066 (N = 268) and **HGS1006-C1074** (N = 733) are ongoing Phase 3, multi-center, continuation studies to evaluate the long-term safety and tolerability of belimumab in subjects with SLE. Subjects who completed Protocol C1056 and C1057 and chose to continue treatment were enrolled in Study C1066 and C1074. All subjects who received belimumab (1 mg/kg or 10 mg/kg) in Study C1056 or C1057 continue to receive the same dose of belimumab every 28 days in the respective continuation trial, while subjects originally randomized to placebo receive 10 mg/kg of belimumab every 28 days.

BEL114333 is an ongoing, Phase 3, multi-center, continuation study to evaluate the long-term safety and tolerability of 10 mg/kg belimumab in subjects who completed Study BEL113750.

BEL112341/HGS1006-C1115 (planned N=816) is an ongoing, Phase 3 multi-center, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of belimumab administered subcutaneously in subjects with SLE. Eligible subjects must have active SLE disease defined as a SELENA-SLEDAI score ≥ 8 and be currently sero-positive for ANA or anti-dsDNA. Subjects must be on a stable standard of care SLE

treatment regimen consisting of any of the following medications (alone or in combination): corticosteroids, antimalarials, NSAIDs, and/or immunosuppressives.

Eligible subjects will be randomized in a 2:1 ratio to either 200 mg belimumab SC weekly or placebo SC weekly in addition to stable standard therapy.

4.5. Treatments

Subjects participating in blinded studies were administered either belimumab (intravenous (IV) or subcutaneous (SC)) or placebo in addition to standard care. Subjects participating in open-label or observational post marketing studies all received belimumab (IV or SC). The primary treatment comparison across exposure groups (1mg/kg IV, 4mg/kg IV, 10mg/kg IV, SC, or placebo) is based on the last dose received prior to or during pregnancy.

Each exposure to belimumab during the time period of interest is captured for all subjects. The time period of interest includes the four months prior to conception and/or during pregnancy duration.

For all clinical trial cases, the level of exposure is categorized as 1mg/kg IV, 4mg/kg IV, 10mg/kg IV or SC by the dose most proximal to the pregnancy onset.

4.5.1. Belimumab Pregnancy Timing

For unblinded clinical studies, spontaneous events and open-label or observational post marketing studies the primary treatment comparison was across belimumab exposure groups based on the last dose received prior to or during pregnancy. Timing of exposure was calculated by adding 100 days (five elimination half-lives of belimumab) to the last belimumab dose. Comparison groups were defined by the following cumulative exposure groups: prior to pregnancy, 0 - 12 $^{6/7}$ weeks gestation, 13 $^{0/7}$ - 26 $^{6/7}$ weeks gestation, or ≥27 $^{0/7}$ weeks gestation. If a patient was started on belimumab during pregnancy such that a cumulative exposure was not applicable, a subgroup would have been incorporated as needed. Analyses were pooled and conducted across dosage and method of drug exposure (intravenous (IV), subcutaneous (SC)).

The gestational age was based on the subject's last menstrual period (when available) except when the expected date of delivery (EDD) was adjusted due to clinical findings (e.g., ultrasound report, physical findings, or clinical information).When a last menstrual period was not reported, the gestational age was based on factors in the following order to identify the most accurate estimate:

- Any gestational age referenced on a specific date (e.g., 35 2/7 weeks gestation on 12 July 2004).
- Any gestational week referenced on a specific date or in a given window of time
- Any narrative detail indicating gestational age

The gestational age was determined by an obstetrician and verified by a healthcare professional.

4.5.2. Treatment Assignment

Subjects were assigned to study treatment based on the most proximal dose of study medication received prior to or during the pregnancy.

4.6. Data Quality Assurance

Each study contributing subjects to the aggregate analysis was conducted according to GCP with details provided outside of .this study.

Subject data was entered into Human Genome Sciences and GSK defined eCRFs, transmitted electronically to GSK and combined with data provided from other sources (e.g., laboratory data) in a validated data system. Investigators were requested to complete a pregnancy initial notification eCRF when the reporting the pregnancy and a pregnancy follow-up eCRF at or shortly after the pregnancy outcome.

SAEs were entered into the database and quality assured, including reconciliation with the GCSP database. Information from the safety case reports was entered into an Excel spreadsheet by a healthcare professional and verified for accuracy by the safety physician.

4.7. Statistical Analyses

All data are summarized using descriptive statistics. Continuous variables are summarized by number of participants, mean, standard deviation (SD), median, lower quartile, upper quartile, minimum and maximum unless otherwise stated. Categorical variables are summarized by number and percentage in each category. Missing data are displayed as a separate category where appropriate. The denominator for all percentages will reflect the number of participants within the cohort, unless otherwise stated (e.g. excluding lost to follow-up (LTF)). All data analyses and reporting were performed using SAS Version 9.3 [SAS Institute Inc., 2011].

For the primary objective (birth defects) and secondary objectives (pregnancy outcomes: live birth, neonatal death, stillbirth, spontaneous miscarriage, elective termination, ectopic pregnancy, and molar pregnancy) prevalence rates and 95% confidence intervals were computed. Confidence intervals for birth defect prevalence were calculated under the exact binomial distribution assumption. . Results were also be stratified by timing of exposure and subgroup.

Birth defects are classified as known chromosomal or syndromic, or specific organ system defect (e.g. cardiovascular, musculoskeletal to include limb defects, urogenital, neural tube defects, gastrointestinal, and other structural defects (including cleft lip and cleft palate)). The prevalence of birth defects was calculated as the percentage of total birth defects total and by organ system from the total number of live births in the study population and then also stratified by subgroup. Fetal losses with reported birth defects occurring at or after 20 weeks gestation were included in the numerator of the estimate of risk for birth defects to increase sensitivity.

Each pregnancy outcome is defined as one of the following: live birth, neonatal death, stillbirth, spontaneous miscarriage, elective termination, ectopic pregnancy, or molar pregnancy. Prevalence rates and 95% confidence intervals were computed for the primary and secondary pregnancy outcomes.

Results are also presented by timing of belimumab exposure for the overall summaries and within each subgroup.

All pregnancy outcomes were summarized by the following subgroups:

- Maternal Age
- Region
- PGA Score (<2 and ≥2)
- SDI (≤1, >1)(
- Concomitant Medications: In each study, background standard therapy for SLE was permitted. The concomitant medications at baseline (clinical trial database) as well as at the time of pregnancy (GSK safety database) were analyzed. Concomitant medications reported at the time of pregnancy were categorized by the following groups:

    - Steroids only,
    - Antimalarial only,
    - Immunosuppressants only
    - Steroids and antimalarials,
    - Steroids and immunosuppressants
    - Antimalarials and immunosuppresents
    - Steroids, antimalarials, and immunosuppressants.
    - Any category D or X medication

  These concomitant medication groups were reviewed and categorized by a healthcare professional and then verified for accuracy by the safety physician.

4.7.1. Analysis Populations

The analytic population includes all pregnancies with an unblinded treatment assignment prior to the 08 March, 2014 data lock point reported in belimumab SLE clinical trials up to 08 March 2014 with a known pregnancy outcome. The demographic analysis also includes subjects that do not have a known pregnancy outcome.

5. STUDY POPULATION RESULTS

5.1. Subject Disposition

Pregnant subjects in clinical trials where treatment was still blinded or the pregnancy was still ongoing (as of 08 March 2014) are not included in the analysis population. If the pregnancy outcome was unknown as of 08 March 2014, the subject was only included in the baseline and demographic analysis but not in the primary or secondary objective analyses.

5.2. Populations Analyzed

There were 77 pregnancies with known outcomes.in 75 women with belimumab exposure. There were 8 pregnancies in 8 women that were randomized to placebo.

5.3. Demographics and Baseline Characteristics

Table 5.01- Table 5.07 describe characteristics available through the completed unblinded clinical trial database. The majority of these tables describe the population's baseline characteristics prior to pregnancy.

5.3.1. Demographics

For the 75 subjects who were exposed to belimumab, the mean age at screening was 27.7 years and mean age at delivery was 30.0 years. The majority of subjects were White [29 (39%)] followed by Asian [22 (29%)] and Alaska Native/ American Indian [10 (13%)] and [32 (43%)] subjects were Hispanic. In addition the majority of subjects were from the United States [21 (28%)] (Table 5.01).

Upon enrolment the average woman's height was 160.6 cm, weight 58.9 kg with a body mass index of 22.7 kg/ m^2 (Table 5.01).

5.3.2. Baseline and Pre-pregnancy disease characteristics

The mean duration since SLE diagnosis was 4.4 years with a standard deviation 3.9 (Table 5.02). The following disease characteristics were summarized in Table 5.02: anti-dsDNA, ANA, C3, C4, SLEDAI, SLICC and PGA.

5.4. Prior and Concomitant Medications

5.4.1. Baseline Medical History

Sixty-seven (89%) of subjects were diagnosed with a medical condition (Table 5.03). The following describes medical conditions which existed in 10% or greater of subjects. The highest reported musculoskeletal/connective tissue disorders included SLE [67 (89%)] (although this was an inclusion criteria), SLE arthritis [29 (39%)] and arthralgia [21 (28%)]. The most often reported skin and subcutaneous disorder were alopecia [34 (45%)], butterfly rash [23 (31%)] and photosensitivity reaction [13 (17%)]. The highest reported vascular disorders were Raynaud's phenomenon [26 (35%)] and hypertension

[14 (19%)]. The highest noted gastrointestinal disorder was Mouth ulceration [15 (20%)]. The most often reported blood and lymphatic system disorders were anaemia [17 (23%)] and leukopenia [10 (13%)] and thrombocytopenia [8 (11%)]. Twenty-eight (37%) subjects had an infection or infestation. The highest reported nervous system disorder were headache [11 (15%)] and migraine [9 (12%)]. Twenty-three (31%) subjects had a respiratory, thoracic and mediastinal disorder, 22 (29%) subjects had a renal and urinary disorder, 16 (21%) subjects had a cardiac disorder, and 13 (17%) subjects had a reproductive system disorder. Twelve (16%) subjects had an eye disorder, 10 (13%) subjects were diagnosed with an endocrine disorder, 10 (13%) subjects were diagnosed with a psychiatric disorder, and 9 (12%) subjects had a hepatobiliary disorder. Less than 10% of subjects were diagnosed with immune system disorder, injury, metabolic/ nutrition disorder, neoplasms, congenital/ familial and genetic disorders, ear and social circumstance (tobacco use).

5.4.2. Concomitant Medication use at Baseline

Forty-four (59%) of subjects were on at least one reported medication at baseline (Table 5.04). The most commonly taken medications (in over 10% of subjects) included hydroxychloroquine [12 (16%)], acetaminophen [11 (15%)], prednisone [9 (12%)], omeprazole [8 (11%)], azathioprine [8 (11%)], and paracetamol [8 (11%)]

5.4.3. Infections

Table 5.05 summarizes the occurrence of infections throughout the clinical trial. Thirty-nine (52%) subjects had at least one infectious AE during participation in the trial. The most common infections were influenza [9 (12%)], nasopharyngitis [8 (11%)] and upper respiratory tract infection [6 (8%)].

5.4.4. Characteristics of Placebo Patients

Eight subjects were randomized to placebo in the clinical trials at the time of the identified pregnancy (Table 5.07). Within the placebo patients the mean age at screening was 29.9 years and mean age at delivery was 31.0 years. The majority of subjects were Asian [3 (38%)] followed by White [2 (25%)], and Alaska Native/American [2 (25%)]. Three (38%) subjects were Hispanic. In addition, the majority of subjects were from either China or Peru each with 2 subjects (25%).

Upon enrolment the average woman's height was 156.6 cm, weight 58.3 kg with a body mass index of 23.8 kg/ m^2.

5.5. Exposure and Treatment Compliance

The primary and secondary outcomes are presented by the following dosing groups 1mg/kg, 4mg/kg, 10mg/kg, subcutaneous, or placebo.

6. RESULTS

6.1. Primary Objective (birth defects)

Table 1.1- Table 1.5 describe the birth defect prevalence per live births (n=38). Of the 38 live births, 4 (11%; 95%CI 3-25%) birth defects were reported, two of which had belimumab exposure through the first trimester and two through the second trimester (Table 1.1). All of these defects were in women <35 years of age at conception, 2 were in North America and 2 outside of North America or Europe. Of these four subjects, 3 subjects were taking 10 mg/kg and 1 subject was taking 1mg/kg (Table 1.2). Table 1.3 shows that 2 of these subjects had a PGA ≥ 2 at the most recent reading prior to pregnancy.

A secondary objective of these analyses was to evaluate concomitant medication use prior to pregnancy. Table 1.4 shows that 3 of pregnancies occurred in patients who were using steroid and anti-malarial, one subject was taking steroids, anti-malarial and an immunosuppressant and one subject was taking a category D or X drug. The subjects with a pregnancy resulting in the chromosomal, neural tube and cardiovascular defects were taking steroids and an antimalarial. The subject with a pregnancy that resulted in a urogenital defect was taking a steroid, antimalarial, immunosuppressant and medication categorized as category D or X.

Birth defects were also broken down by organ system. Of the 4 birth defects one was chromosomal, one was cardiovascular, one was urogenital and one was a neural tube defect (Table 1.5).

Table 2.1- Table 8.4 describe each organ system defect by advanced maternal age, geographic region, dose and concomitant medication. The majority of these tables do not have observations noted since only four birth defects were recorded as of the data cut-off date. Overall all birth defects were all noted to be in women younger than 35 years of age at delivery. Mini-narratives for the four birth defects are included as follows:

MINI-NARRATIVE FOR LIVE BIRTHS WITH A REPORTED CONGENITAL ANOMALY

- [redacted]

- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]

[redacted]

6.2. Secondary Objectives

6.2.1. Birth Outcomes

Table 9 describes the birth secondary outcomes including live birth, preterm birth, term birth, spontaneous miscarriage, stillbirth and elective termination by exposure. Of the 38 (49%; 95% CI 38-61%) live births, 18 were preterm and 20 were term. One (1%; 95%CI <1-7%) of the 77 pregnancies was stillborn while 19 (25%; 95%CI 16-36%) were spontaneous miscarriages and 19 (25%; 95%CI 16-36%) were elective terminations.

6.2.1.1. Live Births

The majority of live births had belimumab exposure through the 2nd trimester [27] (Table 10.1) and occurred in subjects taking 10 mg/kg of belimumab [32] (Table 10.2). Of the 38 live births, 4 pregnancies were to subjects of advanced maternal age (>=35) (Table 10.1). In terms of disease severity, 11 individuals had a PGA >=2 before pregnancy and 9 had an SDI >1 (Table 10.3). Medication usage (provided in the AE report) in live births included six subjects taking a steroid, one subject taking an immunosuppressant, 11 subjects taking a steroid and antimalarial, four subjects taking a steroid and immunosuppressant, one subject taking an immunosuppressant and antimalarial, 13 subjects taking an antimalarial, steroid and immunosuppressant, and 16 subjects taking a category D or X drugs prior/during pregnancy (Table 10.4).

6.2.1.2. Preterm Births

The majority of preterm births (n=18) had belumimab exposure through the 2nd trimester [13] (Table 11.1). Of the 18 preterm births, one pregnancy was in a subject of advanced maternal age (>=35) (Table 11.1). Most preterm births were to subjects taking 10 mg/kg of belimumab [14] (Table 11.2). In terms of disease severity, one subject had a PGA ≥2 before pregnancy and five subject had an SDI >1 (Table 11.3). For medication usage in preterm births, three subjects were taking a steroid, four subjects were taking a steroid and antimalarial, three subjects were taking a steroid and immunosuppressant and nine subjects were taking an antimalarial, steroid and immunosuppressant. Nine subjects with a preterm birth were reported to be taking a category D or X drug when the pregnancy was reported (Table 11.4).

6.2.1.3. Spontaneous Miscarriage

Of the nineteen spontaneous miscarriages, the majority of spontaneous miscarriages had belumimab exposure through the 2nd trimester (14) (Table 12.1) and the majority of these subjects were taking 10mg/kg IV belimumab (14) (Table 12.2). Three of these miscarriages were in subjects of advanced maternal age (≥35) (Table 12.1). In terms of disease severity, 10 individuals had a PGA >=2 before pregnancy and 8 had an SDI >1 (Table 12.3). Medication usage (provided in the AE report) in spontaneous miscarriages included four subjects taking a steroid, eight subjects were taking a steroid and antimalarial, one subject was taking a steroid and immunosuppressant, one subject was

taking an antimalarial, steroid and immunosuppressant, and eight subjects were taking a category D or X drugs prior/during pregnancy (Table 12.4).

6.2.1.4. Stillbirths

Only one stillbirth was reported in the 77 pregnancies. This subject had 10mg/kg exposure through the second trimester, PGA >= 2 and SDI > 1. She developed severe preeclampsia at 27 weeks gestation. A similar outcome occurred in a placebo exposed subject.

6.2.1.5. Elective Abortion

The majority of elective abortions (14) had belimumab exposure through the 2nd trimester and the majority of these subjects (13) were taking 10 mg/kg IV belimumab (Table 14.2). Of the 19 elective abortions, four elective abortions were to subjects of advanced maternal age (≥35) (Table 14.1). In terms of disease severity, 11 subjects had a PGA ≥2 before pregnancy and nine subjects had an SDI >1 (Table 14.3). Medication usage (provided in the AE report) in elective abortions included two subjects taking a steroid, two subjects taking an antimalarial, nine subjects taking a steroid and antimalarial, one subject taking a steroid and immunosuppressant, one subject taking an immunosuppressant and antimalarial, four subjects taking an antimalarial, steroid and immunosuppressant, and seven subjects taking a category D or X drugs prior/during pregnancy (Table 14.4).

6.2.2. Previous Pregnancy History and Outcomes

We additionally described each pregnancy outcome by previously diagnosed pregnancy condition including gravidity, parity, preterm births, term births, spontaneous abortion, stillbirth, and elective termination. The mean previous condition is shown by outcome in Table 2 excluding stillbirth which was only a single event.

Table 2 Summary of Previous Pregnancy Conditions by Pregnancy Outcome

	Pregnancy Outcome									
	Live Birth		Preterm		Term		Spontaneous Miscarriage		Elective Termination	
Previous pregnancy condition	n	mean	n	mean	n	Mean	n	mean	n	mean
Gravidity	27	1.4	13	1.6	14	1.3	10	0.9	15	1.7
Parity	25	0.8	12	0.8	13	0.8	10	0.6	14	1.1
Preterm Births	15	0.6	5	0.4	10	0.7	6	0.0	9	0.2
Term Birth	14	0.0	5	0.0	9	0.0	7	0.4	9	0.3
Spontaneous abortion	16	0.6	8	0.5	0	0.8	5	0.6	4	0.8
Stillbirth	10	0.1	6	0.2	4	0.0	3	0.0	2	0.0
Elective termination	13	0.5	6	0.8	7	0.3	3	0.0	3	0.3

Source: Table 15

6.2.3. Disease Severity

Table 16 described the disease severity prior to pregnancy diagnosis. PGA was reported in 38 live births with a mean score of 1.4 and standard deviation 1.23. SELENA-SLEDAI score was reported in 38 live births with a mean of 5.3 and standard deviation 3.77.

7. DISCUSSION AND CONCLUSIONS

7.1. Discussion

There are several considerations to take into account when contextualizing the experience of belimumab in pregnancy to date.

- There is no reason to predict an IgG antibody would affect organogenesis (which largely completes by the end of first trimester in humans) because the drug is highly specific for BLyS which binds to receptors primarily localized to B lymphocytes and because there is very little placental transfer of IgG antibodies during the first trimester (Simister, 2003).
- Pregnancies in women with SLE are at a higher risk of poor pregnancy outcomes and thus a higher level of surveillance is undertaken to screen for complications. Fetal ultrasound, fetal echocardiogram, and neonatal echocardiogram (particularly with the higher rate of premature birth) are more routinely done compared to the general population. Over the past decade, ultrasound technology has advanced tremendously, enhancing the ability to detect anomalies in utero and after birth (Correa, Cragan et al., 2007). Mild, asymptomatic anomalies that may not have been detected with older technology can now be detected and reported. This is most apparent for certain congenital heart defects, such as ventricular septal defect, atrial septal defect, and valvar pulmonic stenosis (Correa, Cragan et al., 2007). The general population background rates and SLE background rates have an associated lag time that would not reflect these recent enhanced diagnostic capabilities. The extent of this influence is not clear, making it hard to directly compare outcomes to historical rates.
- A recent publication reported that diagnoses of congenital heart defects (CHD) are 3-times more likely (OR = 2.62; 95% CI: 1.77, 3.88) among infants born to women with SLE (5%) compared with the general population (2%); this increased risk has been observed for all types of CHDs (Vinet, 2015)
- SLE treatment commonly includes immunosuppressant therapy thereby increasing the risk of infection to the mother, fetus, and sometimes infant. Certain infections are known to have teratogenic effects including toxoplasmosis, cytomegalovirus, rubella, and parvovirus. It is important to consider potential subclinical infection as a potential mechanism of teratogenicity in this population. However, none of the case reports indicate that infection was present as a confounding issue.
- There are several reports of pregnancy that are either currently ongoing or have been lost to follow-up. There is more likely a bias for pregnancies with negative outcomes to be reported as patients and healthcare providers are considering every potential etiology for that outcome. The pregnancy registry attempts to account for this bias by collecting a cohort of pure prospective pregnancies but will take a long time to accumulate enough experience to draw meaningful conclusions.

Taking these factors into account, there are a few conclusions that can be drawn from this analysis.

Fetal loss including spontaneous miscarriage and stillbirths is consistent with ranges cited in a recent review of pregnancy outcomes in SLE (YanYuen, Krizova et al., 2008). This review of 45 studies cited the range of fetal death from 4% to 43%. The authors commented, "Fetal prognosis corresponds with disease activity, with fetal loss ranging from 25-52% in patients with active SLE compared to 8-12% in patients with inactive SLE at the onset of pregnancy. The latter rate is comparable to observations in healthy women."

At this time, the total number of live births with known outcomes is not sufficient to make quantitative comparison of the total incidence of congenital anomalies relative to another SLE population or the general population. The cases were reviewed in terms of embryological or biological considerations: The case of unbalanced translocation of chromosome 11/13 is not plausibly linked to belimumab because it is not expected that a monoclonal IgG antibody would interact with DNA or chromosomal material Lewis and Cavagnaro, 2010). Of the 3 remaining cases, Dandy Walker Syndrome, renal failure, and pulmonary stenosis are each unique reports.

7.2. Conclusions

- At this time, the total number of live births with known outcomes is not sufficient to make quantitative comparison of the total incidence of congenital anomalies relative to another SLE population or the general population.
- Fetal loss including spontaneous miscarriage and stillbirths is consistent with ranges cited in a recent review of pregnancy outcomes in SLE (Yan Yuen, Krizova et al., 2008). This review of 45 studies cited the range of fetal death from 4% to 43%. The authors commented, "Fetal prognosis corresponds with disease activity, with fetal loss ranging from 25-52% in patients with active SLE compared to 8-12% in patients with inactive SLE at the onset of pregnancy. The latter rate is comparable to observations in healthy women."
- Birth defects and pregnancy outcomes with belimumab exposure are monitored in an ongoing manner to enable detection of any signal that may become apparent over time as the quantity of information grows.
- In addition, the belimumab pregnancy registry is designed to help better understand the risk for congenital anomalies and pregnancy outcomes with belimumab exposure in pregnancy.

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9. LIST OF CLINICAL TRIALS INCLUDED IN AGGREGATE ANALYSIS

Studies included are: BEL110751, BEL110752, BEL112232, BEL112233, BEL112234, BEL112341, BEL113750, BEL114054, BEL114055, BEL114243, BEL114333, BEL114424, BEL114448, BEL115123, BEL115466, BEL115467, BEL115470, BEL115471, BEL116119, BEL116472, HGS1006-C1058, LBRA01, LBRA99, LBSL01_M, LBSL01_S, LBSL02, and LBSL99.

Subject treatment assignments in studies BEL112341, BEL113750, BEL114054, BEL115123, BEL115466, BEL115467 and BEL115471 were blinded as of 08 March, 2015 so they were not included in the analysis.

10. CASE NARRATIVES

There may be minor discrepancies in the details of the SAEs included in the clinical narratives compared with the safety tabulations. This is because the data comes from two different databases (i.e., locked clinical trials database and dynamic SAE database) and has been collected at different points in time. However, all key data points are reconciled. It is considered that these minor discrepancies do not change the overall clinical significance or understanding of the SAE.

Case narratives for the congenital anomaly reports are provided directly in the report in Section 6.1.

Protocol: 201182
Population: Safety

Table 1.1
Summary of Birth Defects
Overall Prevalence and Clinical Study Descriptions

Total number of live births = 38	Overall Birth Defect		Advanced Maternal Age at conception		Geographic Region		
Trimester of exposure	Prevalence	95% CI	< 35	>=35	North America	Europe	Other [1]
Preconception Belimumab Exposure	0		0	0	0	0	0
1st Trimester Belimumab Exposure	2 (5%)	(<1%, 18%)	2 (5%)	0	2 (5%)	0	0
2nd Trimester Belimumab Exposure	2 (5%)	(<1%, 18%)	2 (5%)	0	0	0	2 (5%)
3rd Trimester Belimumab Exposure	0		0	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0		0	0	0	0	0
Any Exposure	4 (11%)	(3%, 25%)	4 (11%)	0	2 (5%)	0	2 (5%)

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

[redacted]

Protocol: 201182
Population: Safety

Table 1.2
Summary of Birth Defects by Belimumab Dose

Total number of live births = 38 Trimester of exposure	Total Pregnancies (N=77)	1 mg/kg	4 mg/kg	10 mg/kg	Subcutaneous Injection	Any Exposure
Preconception Belimumab Exposure	1 (1%)	0	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	1 (3%)	0	1 (3%)	0	2 (5%)
2nd Trimester Belimumab Exposure	56 (73%)	0	0	2 (5%)	0	2 (5%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0	0

[redacted]

Protocol: 201182
Population: Safety

Table 1.3
Summary of Birth Defects by Disease Severity

Total number of live births = 38 Trimester of exposure	Total Pregnancies (N=77)	PGA >=2 before pregnancy	PGA < 2 before pregnancy	SDI > 1 before pregnancy	SDI <= 1 before pregnancy
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	2 (5%)	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	0	0	0	0
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	2 (5%)	0	0	0

[redacted]

Protocol: 201182
Population: Safety

Table 1.4
Summary of Birth Defects by Medication

Total number of birth = 38 Trimester of exposure	Total Pregnancies (N=77)	Steroid [1]	Antimalarial [1]	Immunosuppressant [1]	Steroid + Anti Malarial
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	1 (3%)
2nd Trimester Belimumab Exposure	56 (73%)	0	0	0	2 (5%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	0	0	0	3 (8%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes :Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol, Losartan

[redacted]

Protocol: 201182
Population: Safety

Table 1.4
Summary of Birth Defects by Medication

Total number of birth = 38 Trimester of exposure	Steroid + Immunosuppressant	Immunosuppressant + Anti Malarial	Antimalarial + Steroid + Immunosuppressant	Cat D or X Drug
Preconception Belimumab Exposure	0	0	0	0
1st Trimester Belimumab Exposure	0	0	1 (3%)	1 (3%)
2nd Trimester Belimumab Exposure	0	0	0	0
3rd Trimester Belimumab Exposure	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0	0	0	0
Any Exposure	0	0	1 (3%)	1 (3%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes :Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol, Losartan

[redacted]

Protocol: 201182
Population: Safety

Table 1.5
Summary of Birth Defects by Organ System

Total number of birth = 38 Trimester of exposure	Chromosomal	Cardiovascular	Musculoskeletal	Urogenital	Neural Tube Defect	Gastrointestinal	Other Structural Defect
Preconception Belimumab Exposure	0	0	0	0	0	0	0
1st Trimester Belimumab Exposure	1 (3%)	0	0	1 (3%)	0	0	0
2nd Trimester Belimumab Exposure	0	1 (3%)	0	0	1 (3%)	0	0
3rd Trimester Belimumab Exposure	0	0	0	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0	0	0	0	0	0	0
Any Exposure	1 (3%)	1 (3%)	0	1 (3%)	1 (3%)	0	0

[redacted]

Protocol: 201182
Population: Safety

Table 2.1
Summary of Chromosomal Birth Defects
Overall Prevalence and Clinical Study Descriptions

Total number of live births = 38	Overall Birth Defect			Advanced Maternal Age at conception			Geographic Region					
Trimester of exposure	Prevalence		95% CI	< 35		>=35	North America		Europe	Other [1]		
Preconception Belimumab Exposure	0			0		0	0		0	0		
1st Trimester Belimumab Exposure	1	(3%)	(<1%, 14%)	1	(3%)	0	1	(3%)	0	0		
2nd Trimester Belimumab Exposure	0			0		0	0		0	0		
3rd Trimester Belimumab Exposure	0			0		0	0		0	0		
1st to 2nd Trimester Post-LMP Belimumab Exposure	0			0		0	0		0	0		
Any Exposure	1	(3%)	(<1%, 14%)	1	(3%)	0	1	(3%)	0	0		

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

[redacted]

Protocol: 201182
Population: Safety

Table 2.2
Summary of Chromosomal Birth Defects by Belimumab Dose

Total number of live births = 38

Trimester of exposure	Total Pregnancies (N=77)	1 mg/kg	4 mg/kg	10 mg/kg	Subcutaneous Injection	Any Exposure
Preconception Belimumab Exposure	1 (1%)	0	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	1 (3%)	0	1 (3%)
2nd Trimester Belimumab Exposure	56 (73%)	0	0	0	0	0
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0	0

[redacted]

Protocol: 201182
Population: Safety

Table 2.3
Summary of Chromosomal Birth Defects by Disease Severity

Total number of live births = 38 Trimester of exposure	Total Pregnancies (N=77)	PGA >=2 before pregnancy	PGA < 2 before pregnancy	SDI > 1 before pregnancy	SDI <= 1 before pregnancy
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	1 (3%)	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	0	0	0	0
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	1 (3%)	0	0	0

[redacted]

Protocol: 201182
Population: Safety

Table 2.4
Summary of Chromosomal Birth Defects by Medication

Total number of live births = 38 Trimester of exposure	Total Pregnancies (N=77)	Steroid [1]	Antimalarial [1]	Immunosuppressant [1]	Steroid + Anti Malarial
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	1 (3%)
2nd Trimester Belimumab Exposure	56 (73%)	0	0	0	0
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	0	0	0	1 (3%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 2.4
Summary of Chromosomal Birth Defects by Medication

Total number of live births = 38 Trimester of exposure	Steroid + Immunosuppressant	Immunosuppressant + Anti Malarial	Antimalarial + Steroid + Immunosuppressant	Cat D or X Drug
Preconception Belimumab Exposure	0	0	0	0
1st Trimester Belimumab Exposure	0	0	0	0
2nd Trimester Belimumab Exposure	0	0	0	0
3rd Trimester Belimumab Exposure	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0	0	0	0
Any Exposure	0	0	0	0

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 3.1
Summary of Cardiovascular Birth Defects
Overall Prevalence and Clinical Study Descriptions

Total number of live births = 38	Overall Birth Defect		Advanced Maternal Age at conception		Geographic Region		
Trimester of exposure	Prevalence	95% CI	< 35	>=35	North America	Europe	Other [1]
Preconception Belimumab Exposure	0		0	0	0	0	0
1st Trimester Belimumab Exposure	0		0	0	0	0	0
2nd Trimester Belimumab Exposure	1 (3%)	(<1%, 14%)	1 (3%)	0	0	0	1 (3%)
3rd Trimester Belimumab Exposure	0		0	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0		0	0	0	0	0
Any Exposure	1 (3%)	(<1%, 14%)	1 (3%)	0	0	0	1 (3%)

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

[redacted]

Protocol: 201182
Population: Safety

Table 3.2
Summary of Cardiovascular Birth Defects by Belimumab Dose

Total number of live births = 38

Trimester of exposure	Total Pregnancies (N=77)	1 mg/kg	4 mg/kg	10 mg/kg	Subcutaneous Injection	Any Exposure
Preconception Belimumab Exposure	1 (1%)	0	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	0	0	1 (3%)	0	1 (3%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0	0

[redacted]

Protocol: 201182
Population: Safety

Table 3.3
Summary of Cardiovascular Birth Defects by Disease Severity

No Data to report

[redacted]

Protocol: 201182
Population: Safety

Table 3.4
Summary of Cardiovascular Birth Defects by Medication

Total number of live births = 38 Trimester of exposure	Total Pregnancies (N=77)	Steroid [1]	Antimalarial [1]	Immunosuppressant [1]	Steroid + Anti Malarial
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	0	0	0	1 (3%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	0	0	0	1 (3%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 3.4
Summary of Cardiovascular Birth Defects by Medication

Total number of live births = 38 Trimester of exposure	Steroid + Immunosuppressant	Immunosuppressant + Anti Malarial	Antimalarial + Steroid + Immunosuppressant	Cat D or X Drug
Preconception Belimumab Exposure	0	0	0	0
1st Trimester Belimumab Exposure	0	0	0	0
2nd Trimester Belimumab Exposure	0	0	0	0
3rd Trimester Belimumab Exposure	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0	0	0	0
Any Exposure	0	0	0	0

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 4.1
Summary of Musculoskeletal Birth Defects
Overall Prevalence and Clinical Study Descriptions

No Data to report

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

Protocol: 201182
Population: Safety

Table 4.2
Summary of Musculoskeletal Birth Defects by Belimumab Dose

No Data to report

[redacted]

Protocol: 201182
Population: Safety

Table 4.3
Summary of Musculoskeletal Birth Defects by Disease Severity

No Data to report

[redacted]

Protocol: 201182
Population: Safety

Table 4.4
Summary of Musculoskeletal Birth Defects by Medication

No Data to report

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 5.1
Summary of Urogenital Birth Defects
Overall Prevalence and Clinical Study Descriptions

Total number of live births = 38	Overall Birth Defect			Advanced Maternal Age at conception			Geographic Region				
Trimester of exposure	Prevalence		95% CI	< 35		>=35	North America		Europe	Other [1]	
Preconception Belimumab Exposure	0			0		0	0		0	0	
1st Trimester Belimumab Exposure	1	(3%)	(<1%, 14%)	1	(3%)	0	1	(3%)	0	0	
2nd Trimester Belimumab Exposure	0			0		0	0		0	0	
3rd Trimester Belimumab Exposure	0			0		0	0		0	0	
1st to 2nd Trimester Post-LMP Belimumab Exposure	0			0		0	0		0	0	
Any Exposure	1	(3%)	(<1%, 14%)	1	(3%)	0	1	(3%)	0	0	

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

[redacted]

Protocol: 201182
Population: Safety

Table 5.2
Summary of Urogenital Birth Defects by Belimumab Dose

Total number of live births = 38

Trimester of exposure	Total Pregnancies (N=77)	1 mg/kg	4 mg/kg	10 mg/kg	Subcutaneous Injection	Any Exposure
Preconception Belimumab Exposure	1 (1%)	0	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	1 (3%)	0	0	0	1 (3%)
2nd Trimester Belimumab Exposure	56 (73%)	0	0	0	0	0
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0	0

[redacted]

Protocol: 201182
Population: Safety

Table 5.3
Summary of Urogenital Birth Defects by Disease Severity

Total number of live births = 38 Trimester of exposure	Total Pregnancies (N=77)	PGA >=2 before pregnancy	PGA < 2 before pregnancy	SDI > 1 before pregnancy	SDI <= 1 before pregnancy
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	1 (3%)	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	0	0	0	0
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	1 (3%)	0	0	0

[redacted]

Protocol: 201182
Population: Safety

Table 5.4
Summary of Urogenital Birth Defects by Medication

Total number of live births = 38 Trimester of exposure	Total Pregnancies (N=77)	Steroid [1]	Antimalarial [1]	Immunosuppressant [1]	Steroid + Anti Malarial
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	0	0	0	0
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	0	0	0	0

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 5.4
Summary of Urogenital Birth Defects by Medication

Total number of live births = 38 Trimester of exposure	Steroid + Immunosuppressant	Immunosuppressant + Anti Malarial	Antimalarial + Steroid + Immunosuppressant	Cat D or X Drug
Preconception Belimumab Exposure	0	0	0	0
1st Trimester Belimumab Exposure	0	0	1 (3%)	1 (3%)
2nd Trimester Belimumab Exposure	0	0	0	0
3rd Trimester Belimumab Exposure	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0	0	0	0
Any Exposure	0	0	1 (3%)	1 (3%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 6.1
Summary of Neural Tube Birth Defects
Overall Prevalence and Clinical Study Descriptions

Total number of live births = 38	Overall Birth Defect			Advanced Maternal Age at conception		Geographic Region		
Trimester of exposure	Prevalence		95% CI	< 35	>=35	North America	Europe	Other [1]
Preconception Belimumab Exposure	0			0	0	0	0	0
1st Trimester Belimumab Exposure	0			0	0	0	0	0
2nd Trimester Belimumab Exposure	1	(3%)	(<1%, 14%)	1 (3%)	0	0	0	1 (3%)
3rd Trimester Belimumab Exposure	0			0	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0			0	0	0	0	0
Any Exposure	1	(3%)	(<1%, 14%)	1 (3%)	0	0	0	1 (3%)

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

[redacted]

Protocol: 201182
Population: Safety

Table 6.2
Summary of Neural Tube Birth Defects by Belimumab Dose

Total number of live births = 38

Trimester of exposure	Total Pregnancies (N=77)	1 mg/kg	4 mg/kg	10 mg/kg	Subcutaneous Injection	Any Exposure
Preconception Belimumab Exposure	1 (1%)	0	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	0	0	1 (3%)	0	1 (3%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0	0

[redacted]

Protocol: 201182
Population: Safety

Table 6.3
Summary of Neural Tube Birth Defects by Disease Severity

No Data to report

[redacted]

Protocol: 201182
Population: Safety

Table 6.4
Summary of Neural Tube Birth Defects by Medication

Total number of live births = 38 Trimester of exposure	Total Pregnancies (N=77)	Steroid [1]	Antimalarial [1]	Immunosuppressant [1]	Steroid + Anti Malarial
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	0	0	0	1 (3%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	0	0	0	1 (3%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 6.4
Summary of Neural Tube Birth Defects by Medication

Total number of live births = 38 Trimester of exposure	Steroid + Immunosuppressant	Immunosuppressant + Anti Malarial	Antimalarial + Steroid + Immunosuppressant	Cat D or X Drug
Preconception Belimumab Exposure	0	0	0	0
1st Trimester Belimumab Exposure	0	0	0	0
2nd Trimester Belimumab Exposure	0	0	0	0
3rd Trimester Belimumab Exposure	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0	0	0	0
Any Exposure	0	0	0	0

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 7.1
Summary of Gastrointestinal Birth Defects
Overall Prevalence and Clinical Study Descriptions

No Data to report

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

Protocol: 201182
Population: Safety

Table 7.2
Summary of Gastrointestinal Birth Defects by Belimumab Dose

No Data to report

[redacted]

Protocol: 201182
Population: Safety

Table 7.3
Summary of Gastrointestinal Birth Defects by Disease Severity

No Data to report

Protocol: 201182
Population: Safety

Table 7.4
Summary of Gastrointestinal Birth Defects by Medication

No Data to report

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 8.1
Summary of Other Structural Birth Defects
Overall Prevalence and Clinical Study Descriptions

No Data to report

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

Protocol: 201182
Population: Safety

Table 8.2
Summary of Other Structural Birth Defects by Belimumab Dose

No Data to report

[redacted]

Protocol: 201182
Population: Safety

Table 8.3
Summary of Other Structural Birth Defects by Disease Severity

No Data to report

[redacted]

Protocol: 201182
Population: Safety

Table 8.4
Summary of Other Structural Birth Defects by Medication

No Data to report

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

Protocol: 201182
Population: Safety

Table 9
Summary of Birth Outcomes

Total number of pregnancies = 77

Trimester of exposure	Live Births	Preterm Births	Term Births	Spontaneous Miscarriage	Stillbirth	Elective Termination
Preconception Belimumab Exposure	0	0	0	0	0	1 (1%)
1st Trimester Belimumab Exposure	9 (12%)	5 (6%)	4 (5%)	2 (3%)	0	0
2nd Trimester Belimumab Exposure	27 (35%)	13 (17%)	14 (18%)	14 (18%)	1 (1%)	14 (18%)
3rd Trimester Belimumab Exposure	1 (1%)	0	1 (1%)	3 (4%)	0	2 (3%)
1st to 2nd Trimester Post-LMP Belimumab Exposure	1 (1%)	0	1 (1%)	0	0	2 (3%)
Any Exposure	38 (49%)	18 (23%)	20 (26%)	19 (25%)	1 (1%)	19 (25%)

[redacted]

Protocol: 201182
Population: Safety

Table 10.1
Summary of Live Births
Overall Prevalence and Clinical Study Descriptions

Total number of pregnancies = 77	Overall Live Birth		Advanced Maternal Age at conception		Geographic Region		
Trimester of exposure	Prevalence	95% CI	< 35	>=35	North America	Europe	Other [1]
Preconception Belimumab Exposure	0		0	0	0	0	0
1st Trimester Belimumab Exposure	9 (12%)	(5%, 21%)	8 (10%)	1 (1%)	5 (6%)	0	4 (5%)
2nd Trimester Belimumab Exposure	27 (35%)	(25%, 47%)	24 (31%)	3 (4%)	6 (8%)	4 (5%)	17 (22%)
3rd Trimester Belimumab Exposure	1 (1%)	(<1%, 7%)	1 (1%)	0	1 (1%)	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	1 (1%)	(<1%, 7%)	1 (1%)	0	1 (1%)	0	0
Any Exposure	38 (49%)	(38%, 61%)	34 (44%)	4 (5%)	13 (17%)	4 (5%)	21 (27%)

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

[redacted]

Protocol: 201182
Population: Safety

Table 10.2
Summary of Live Births by Belimumab Dose

Total number of pregnancies = 77

Trimester of exposure	Total Pregnancies (N=77)	1 mg/kg	4 mg/kg	10 mg/kg	Subcutaneous Injection	Any Exposure
Preconception Belimumab Exposure	1 (1%)	0	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	3 (4%)	0	6 (8%)	0	9 (12%)
2nd Trimester Belimumab Exposure	56 (73%)	3 (4%)	0	24 (31%)	0	27 (35%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	1 (1%)	0	1 (1%)
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	1 (1%)	0	1 (1%)

[redacted]

Protocol: 201182
Population: Safety

Table 10.3
Summary of Live Births by Disease Severity

Total number of pregnancies = 77 Trimester of exposure	Total Pregnancies (N=77)	PGA >=2 before pregnancy	PGA < 2 before pregnancy	SDI > 1 before pregnancy	SDI <= 1 before pregnancy
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	5 (6%)	0	3 (4%)	1 (1%)
2nd Trimester Belimumab Exposure	56 (73%)	5 (6%)	2 (3%)	6 (8%)	2 (3%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	1 (1%)	0	0	0
Any Exposure	77(100%)	11 (14%)	2 (3%)	9 (12%)	3 (4%)

[redacted]

Protocol: 201182
Population: Safety

Table 10.4
Summary of Live Births by Medication

Total number of pregnancies = 77 Trimester of exposure	Total Pregnancies (N=77)	Steroid [1]	Antimalarial [1]	Immunosuppressant [1]	Steroid + Anti Malarial
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	1 (1%)
2nd Trimester Belimumab Exposure	56 (73%)	6 (8%)	1 (1%)	0	9 (12%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	1 (1%)
Any Exposure	77(100%)	6 (8%)	1 (1%)	0	11 (14%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 10.4
Summary of Live Births by Medication

Total number of pregnancies = 77 Trimester of exposure	Steroid + Immunosuppressant	Immunosuppressant + Anti Malarial	Antimalarial + Steroid + Immunosuppressant	Cat D or X Drug
Preconception Belimumab Exposure	0	0	0	0
1st Trimester Belimumab Exposure	0	1 (1%)	6 (8%)	5 (6%)
2nd Trimester Belimumab Exposure	4 (5%)	0	6 (8%)	10 (13%)
3rd Trimester Belimumab Exposure	0	0	1 (1%)	1 (1%)
1st to 2nd Trimester Post-LMP Belimumab Exposure	0	0	0	0
Any Exposure	4 (5%)	1 (1%)	13 (17%)	16 (21%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 11.1
Summary of Preterm Births
Overall Prevalence and Clinical Study Descriptions

Total number of pregnancies = 77	Overall Preterm Birth		Advanced Maternal Age at conception		Geographic Region		
Trimester of exposure	Prevalence	95% CI	< 35	>=35	North America	Europe	Other [1]
Preconception Belimumab Exposure	0		0	0	0	0	0
1st Trimester Belimumab Exposure	5 (6%)	(2%, 15%)	4 (5%)	1 (1%)	4 (5%)	0	1 (1%)
2nd Trimester Belimumab Exposure	13 (17%)	(9%, 27%)	13 (17%)	0	3 (4%)	2 (3%)	8 (10%)
3rd Trimester Belimumab Exposure	0		0	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0		0	0	0	0	0
Any Exposure	18 (23%)	(14%, 34%)	17 (22%)	1 (1%)	7 (9%)	2 (3%)	9 (12%)

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

[redacted]

Protocol: 201182
Population: Safety

Table 11.2
Summary of Preterm Births by Belimumab Dose

Total number of pregnancies = 77

Trimester of exposure	Total Pregnancies (N=77)	1 mg/kg	4 mg/kg	10 mg/kg	Subcutaneous Injection	Any Exposure
Preconception Belimumab Exposure	1 (1%)	0	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	2 (3%)	0	3 (4%)	0	5 (6%)
2nd Trimester Belimumab Exposure	56 (73%)	2 (3%)	0	11 (14%)	0	13 (17%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0	0

[redacted]

Protocol: 201182
Population: Safety

Table 11.3
Summary of Preterm Births by Disease Severity

Total number of pregnancies = 77

Trimester of exposure	Total Pregnancies (N=77)	PGA >=2 before pregnancy	PGA < 2 before pregnancy	SDI > 1 before pregnancy	SDI <= 1 before pregnancy
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	4 (5%)	0	1 (1%)	1 (1%)
2nd Trimester Belimumab Exposure	56 (73%)	3 (4%)	1 (1%)	4 (5%)	0
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	7 (9%)	1 (1%)	5 (6%)	1 (1%)

[redacted]

Protocol: 201182
Population: Safety

Table 11.4
Summary of Preterm Births by Medication

Total number of pregnancies = 77 Trimester of exposure	Total Pregnancies (N=77)	Steroid [1]	Antimalarial [1]	Immunosuppressant [1]	Steroid + Anti Malarial
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	1 (1%)
2nd Trimester Belimumab Exposure	56 (73%)	3 (4%)	0	0	3 (4%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	3 (4%)	0	0	4 (5%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 11.4
Summary of Preterm Births by Medication

Total number of pregnancies = 77 Trimester of exposure	Steroid + Immunosuppressant	Immunosuppressant + Anti Malarial	Antimalarial + Steroid + Immunosuppressant	Cat D or X Drug
Preconception Belimumab Exposure	0	0	0	0
1st Trimester Belimumab Exposure	0	0	3 (4%)	3 (4%)
2nd Trimester Belimumab Exposure	3 (4%)	0	4 (5%)	6 (8%)
3rd Trimester Belimumab Exposure	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0	0	0	0
Any Exposure	3 (4%)	0	7 (9%)	9 (12%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 12.1
Summary of Spontaneous Miscarriages
Overall Prevalence and Clinical Study Descriptions

Total number of pregnancies = 77	Overall Spontaneous Miscarriage		Advanced Maternal Age at conception		Geographic Region		
Trimester of exposure	Prevalence	95% CI	< 35	>=35	North America	Europe	Other [1]
Preconception Belimumab Exposure	0		0	0	0	0	0
1st Trimester Belimumab Exposure	2 (3%)	(<1%, 9%)	2 (3%)	0	2 (3%)	0	0
2nd Trimester Belimumab Exposure	14 (18%)	(10%, 29%)	12 (16%)	2 (3%)	3 (4%)	0	11 (14%)
3rd Trimester Belimumab Exposure	3 (4%)	(<1%, 11%)	2 (3%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
1st to 2nd Trimester Post-LMP Belimumab Exposure	0		0	0	0	0	0
Any Exposure	19 (25%)	(16%, 36%)	16 (21%)	3 (4%)	6 (8%)	1 (1%)	12 (16%)

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

[redacted]

Protocol: 201182
Population: Safety

Table 12.2
Summary of Spontaneous Miscarriages by Belimumab Dose

Total number of pregnancies = 77

Trimester of exposure	Total Pregnancies (N=77)	1 mg/kg	4 mg/kg	10 mg/kg	Subcutaneous Injection	Any Exposure
Preconception Belimumab Exposure	1 (1%)	0	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	1 (1%)	1 (1%)	0	0	2 (3%)
2nd Trimester Belimumab Exposure	56 (73%)	1 (1%)	0	13 (17%)	0	14 (18%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	1 (1%)	2 (3%)	3 (4%)
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0	0

[redacted]

Protocol: 201182
Population: Safety

Table 12.3
Summary of Spontaneous Miscarriages by Disease Severity

Total number of pregnancies = 77 Trimester of exposure	Total Pregnancies (N=77)	PGA >=2 before pregnancy	PGA < 2 before pregnancy	SDI > 1 before pregnancy	SDI <= 1 before pregnancy
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	2 (3%)	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	8 (10%)	0	7 (9%)	0
3rd Trimester Belimumab Exposure	6 (8%)	0	2 (3%)	1 (1%)	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	10 (13%)	2 (3%)	8 (10%)	0

[redacted]

Protocol: 201182
Population: Safety

Table 12.4
Summary of Spontaneous Miscarriages by Medication

Total number of pregnancies = 77 Trimester of exposure	Total Pregnancies (N=77)	Steroid [1]	Antimalarial [1]	Immunosuppressant [1]	Steroid + Anti Malarial
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	2 (3%)	1 (1%)	0	7 (9%)
3rd Trimester Belimumab Exposure	6 (8%)	2 (3%)	0	0	1 (1%)
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	4 (5%)	1 (1%)	0	8 (10%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 12.4
Summary of Spontaneous Miscarriages by Medication

Total number of pregnancies = 77 Trimester of exposure	Steroid + Immunosuppressant	Immunosuppressant + Antimalarial	Antimalarial + Steroid + Immunosuppressant	Cat D or X Drug
Preconception Belimumab Exposure	0	0	0	0
1st Trimester Belimumab Exposure	0	0	0	1 (1%)
2nd Trimester Belimumab Exposure	1 (1%)	0	2 (3%)	7 (9%)
3rd Trimester Belimumab Exposure	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0	0	0	0
Any Exposure	1 (1%)	0	2 (3%)	8 (10%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 13.1
Summary of Stillbirths
Overall Prevalence and Clinical Study Descriptions

Total number of pregnancies = 77	Overall Still Birth			Advanced Maternal Age at conception			Geographic Region				
Trimester of exposure	Prevalence		95% CI	< 35		>=35	North America	Europe	Other [1]		
Preconception Belimumab Exposure	0			0		0	0	0	0		
1st Trimester Belimumab Exposure	0			0		0	0	0	0		
2nd Trimester Belimumab Exposure	1	(1%)	(<1%, 7%)	1	(1%)	0	0	0	1	(1%)	
3rd Trimester Belimumab Exposure	0			0		0	0	0	0		
1st to 2nd Trimester Post-LMP Belimumab Exposure	0			0		0	0	0	0		
Any Exposure	1	(1%)	(<1%, 7%)	1	(1%)	0	0	0	1	(1%)	

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

[redacted]

Protocol: 201182
Population: Safety

Table 13.2
Summary of Stillbirths by Belimumab Dose

Total number of pregnancies = 77

Trimester of exposure	Total Pregnancies (N=77)	1 mg/kg	4 mg/kg	10 mg/kg	Subcutaneous Injection	Any Exposure
Preconception Belimumab Exposure	1 (1%)	0	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	0	0	1 (1%)	0	1 (1%)
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0	0

[redacted]

Protocol: 201182
Population: Safety

Table 13.3
Summary of Stillbirths by Disease Severity

Total number of pregnancies = 77 Trimester of exposure	Total Pregnancies (N=77)	PGA >=2 before pregnancy	PGA < 2 before pregnancy	SDI > 1 before pregnancy	SDI <= 1 before pregnancy
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	1 (1%)	0	1 (1%)	0
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	1 (1%)	0	1 (1%)	0

[redacted]

Protocol: 201182
Population: Safety

Table 13.4
Summary of Stillbirths by Medication

Total number of pregnancies = 77 Trimester of exposure	Total Pregnancies (N=77)	Steroid [1]	Antimalarial [1]	Immunosuppressant [1]	Steroid + Anti Malarial
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	1 (1%)	0	0	0
3rd Trimester Belimumab Exposure	6 (8%)	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	0
Any Exposure	77(100%)	1 (1%)	0	0	0

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 13.4
Summary of Stillbirths by Medication

Total number of pregnancies = 77 Trimester of exposure	Steroid + Immunosuppressant	Immunosuppressant + Anti Malarial	Antimalarial + Steroid + Immunosuppressant	Cat D or X Drug
Preconception Belimumab Exposure	0	0	0	0
1st Trimester Belimumab Exposure	0	0	0	0
2nd Trimester Belimumab Exposure	0	0	0	0
3rd Trimester Belimumab Exposure	0	0	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	0	0	0	0
Any Exposure	0	0	0	0

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 14.1
Summary of Elective Abortions
Overall Prevalence and Clinical Study Descriptions

Total number of pregnancies = 77	Overall Elective Abortion		Advanced Maternal Age at conception		Geographic Region		
Trimester of exposure	Prevalence	95% CI	< 35	>=35	North America	Europe	Other [1]
Preconception Belimumab Exposure	1 (1%)	(<1%, 7%)	1 (1%)	0	1 (1%)	0	0
1st Trimester Belimumab Exposure	0		0	0	0	0	0
2nd Trimester Belimumab Exposure	14 (18%)	(10%, 29%)	10 (13%)	4 (5%)	2 (3%)	3 (4%)	9 (12%)
3rd Trimester Belimumab Exposure	2 (3%)	(<1%, 9%)	2 (3%)	0	1 (1%)	1 (1%)	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	2 (3%)	(<1%, 9%)	2 (3%)	0	0	0	2 (3%)
Any Exposure	19 (25%)	(16%, 36%)	15 (19%)	4 (5%)	4 (5%)	4 (5%)	11 (14%)

[1] Other geographic region includes Asia, South America and Mexico
Groups are defined by cumulative exposure through pregnancy(SEE RAP)

[redacted]

Protocol: 201182
Population: Safety

Table 14.2
Summary of Elective Abortion by Belimumab Dose

Total number of pregnancies = 77

Trimester of exposure	Total Pregnancies (N=77)	1 mg/kg	4 mg/kg	10 mg/kg	Subcutaneous Injection	Any Exposure
Preconception Belimumab Exposure	1 (1%)	0	1 (1%)	0	0	1 (1%)
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	3 (4%)	0	11 (14%)	0	14 (18%)
3rd Trimester Belimumab Exposure	6 (8%)	1 (1%)	0	0	1 (1%)	2 (3%)
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	2 (3%)	0	2 (3%)

[redacted]

Protocol: 201182
Population: Safety

Table 14.3
Summary of Elective Abortions by Disease Severity

Total number of pregnancies = 77

Trimester of exposure	Total Pregnancies (N=77)	PGA >=2 before pregnancy	PGA < 2 before pregnancy	SDI > 1 before pregnancy	SDI <= 1 before pregnancy
Preconception Belimumab Exposure	1 (1%)	1 (1%)	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	8 (10%)	0	9 (12%)	1 (1%)
3rd Trimester Belimumab Exposure	6 (8%)	1 (1%)	1 (1%)	0	0
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	1 (1%)	0	0	0
Any Exposure	77(100%)	11 (14%)	1 (1%)	9 (12%)	1 (1%)

[redacted]

Protocol: 201182
Population: Safety

Table 14.4
Summary of Elective Abortions by Medication

Total number of pregnancies = 77 Trimester of exposure	Total Pregnancies (N=77)	Steroid [1]	Antimalarial [1]	Immunosuppressant [1]	Steroid + Anti Malarial
Preconception Belimumab Exposure	1 (1%)	0	0	0	0
1st Trimester Belimumab Exposure	11 (14%)	0	0	0	0
2nd Trimester Belimumab Exposure	56 (73%)	2 (3%)	1 (1%)	0	6 (8%)
3rd Trimester Belimumab Exposure	6 (8%)	0	1 (1%)	0	1 (1%)
1st to 2nd Trimester Post-LMP Belimumab Exposure	3 (4%)	0	0	0	2 (3%)
Any Exposure	77(100%)	2 (3%)	2 (3%)	0	9 (12%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 14.4
Summary of Elective Abortions by Medication

Total number of pregnancies = 77 Trimester of exposure	Steroid + Immunosuppressant	Immunosuppressant + Anti Malarial	Antimalarial + Steroid + Immunosuppressant	Cat D or X Drug
Preconception Belimumab Exposure	0	1 (1%)	0	1 (1%)
1st Trimester Belimumab Exposure	0	0	0	0
2nd Trimester Belimumab Exposure	1 (1%)	0	4 (5%)	4 (5%)
3rd Trimester Belimumab Exposure	0	0	0	1 (1%)
1st to 2nd Trimester Post-LMP Belimumab Exposure	0	0	0	1 (1%)
Any Exposure	1 (1%)	1 (1%)	4 (5%)	7 (9%)

[1] Steroid, Antimalarial, and Immunosuppressant use independently
Category D+X drug includes : Methotrexate, Tretinoin, Mycophenolate, Azathioprine, Enalapril, Lisinopril, Captopril, Valproic acid, Atorvastatin, Simvastatin, Fluconazole, Thalidomide, Ambrisentan, Lorazepam, Etizolam, Thiamazole, Atenolol and Losartan.

[redacted]

Protocol: 201182
Population: Safety

Table 15
Summary of Previous Pregnancy Conditions by Birth Outcome

Previous Pregnancy Condition		Live Births (N=38)	Preterm (N=18)	Term (N=20)	Spontaneous Miscarriage (N=19)	Stillbirth (N=1)	Elective Termination (N=19)
Gravidity	n	27	13	14	10	0	15
	Mean	1.4	1.6	1.3	0.9		1.7
	SD	1.48	1.19	1.73	0.99		1.99
	Median	1.0	1.0	1.0	1.0		1.0
	Min.	0	0	0	0		0
	Max.	5	4	5	3		8
	Q1	0	1	0	0		0
	Q3	2	2	2	1		2
Parity	n	25	12	13	10	0	14
	Mean	0.8	0.8	0.8	0.6		1.1
	SD	1.05	0.97	1.17	0.52		1.33
	Median	0.0	0.5	0.0	1.0		1.0
	Min.	0	0	0	0		0
	Max.	3	3	3	1		5
	Q1	0	0	0	0		0
	Q3	1	1	1	1		1
Preterm Birth	n	15	5	10	6	0	9
	Mean	0.6	0.4	0.7	0.0		0.2
	SD	1.06	0.55	1.25	0.00		0.44
	Median	0.0	0.0	0.0	0.0		0.0
	Min.	0	0	0	0		0
	Max.	3	1	3	0		1
	Q1	0	0	0	0		0
	Q3	1	1	1	0		0

[redacted]

Protocol: 201182
Population: Safety

Table 15
Summary of Previous Pregnancy Conditions by Birth Outcome

Previous Pregnancy Condition		Live Births (N=38)	Preterm (N=18)	Term (N=20)	Spontaneous Miscarriage (N=19)	Stillbirth (N=1)	Elective Termination (N=19)
Term Birth	n	14	5	9	7	0	9
	Mean	0.0	0.0	0.0	0.4		0.3
	SD	0.00	0.00	0.00	0.53		0.71
	Median	0.0	0.0	0.0	0.0		0.0
	Min.	0	0	0	0		0
	Max.	0	0	0	1		2
	Q1	0	0	0	0		0
	Q3	0	0	0	1		0
Spontaneous Abortion	n	16	8	8	5	0	4
	Mean	0.6	0.5	0.8	0.6		0.8
	SD	0.72	0.53	0.89	0.89		0.96
	Median	0.5	0.5	0.5	0.0		0.5
	Min.	0	0	0	0		0
	Max.	2	1	2	2		2
	Q1	0	0	0	0		0
	Q3	1	1	2	1		2
Stillbirth	n	10	6	4	3	0	2
	Mean	0.1	0.2	0.0	0.0		0.0
	SD	0.32	0.41	0.00	0.00		0.00
	Median	0.0	0.0	0.0	0.0		0.0
	Min.	0	0	0	0		0
	Max.	1	1	0	0		0
	Q1	0	0	0	0		0
	Q3	0	0	0	0		0

[redacted]

Protocol: 201182
Population: Safety

Table 15
Summary of Previous Pregnancy Conditions by Birth Outcome

Previous Pregnancy Condition		Live Births (N=38)	Preterm (N=18)	Term (N=20)	Spontaneous Miscarriage (N=19)	Stillbirth (N=1)	Elective Termination (N=19)
Elective Termination	n	13	6	7	3	0	3
	Mean	0.5	0.8	0.3	0.0		0.3
	SD	0.97	1.33	0.49	0.00		0.58
	Median	0.0	0.0	0.0	0.0		0.0
	Min.	0	0	0	0		0
	Max.	3	3	1	0		1
	Q1	0	0	0	0		0
	Q3	1	2	1	0		1

[redacted]

Protocol: 201182
Population: Safety

Table 16
Summary of Disease Severity
Descriptive Statistics

Disease Severity	Total Number of pregnancies	n	Mean	SD	Median	Min.	Max.	Q1	Q3
PGA	77	38	1.4	1.23	1.0	0	6	1	2
SELENA SLEDAI	77	75	5.3	3.77	4.0	0	21	2	8

[redacted]

Protocol: 201182
Population: Safety

Table 5.01
Summary of Demographic Characteristics

		Total (N=75)
Age at screening (y)	n	75
	Mean	27.7
	SD	5.07
	Median	27.0
	Min.	18
	Max.	44
Age at delivery (y)	n	75
	Mean	30.0
	SD	5.01
	Median	29.0
	Min.	20
	Max.	45
Age Group 1 at delivery	n	75
	20-24 Years	8 (11%)
	25-29 Years	33 (44%)
	30-34 Years	20 (27%)
	35-39 Years	12 (16%)
	40-44 Years	1 (1%)
	45-49 Years	1 (1%)
Age Group 2 at delivery	n	75
	<35 Years	61 (81%)
	>=35 Years	14 (19%)
Race	n	75
	White	29 (39%)
	Black or African American	5 (7%)
	Asian	22 (29%)
	Alaska Native or American Indian	10 (13%)
	Native Hawaiian or Other Pacific Islander	9 (12%)

[redacted]

Protocol: 201182
Population: Safety

Table 5.01
Summary of Demographic Characteristics

		Total (N=75)
Ethnicity	n	75
	Hispanic or Latino	32 (43%)
	Not Hispanic or Latino	43 (57%)
Country	n	75
	Argentina	8 (11%)
	Belgium	1 (1%)
	Brazil	1 (1%)
	China	3 (4%)
	Colombia	10 (13%)
	Germany	1 (1%)
	Israel	1 (1%)
	Japan	1 (1%)
	Korea	3 (4%)
	Mexico	4 (5%)
	Philippines	9 (12%)
	Poland	1 (1%)
	Romania	2 (3%)
	Russia	3 (4%)
	Taiwan	5 (7%)
	Ukraine	1 (1%)
	United States	21 (28%)
Height (cm)	n	75
	Mean	160.6
	SD	7.24
	Median	160.0
	Min.	145
	Max.	180

[redacted]

Protocol: 201182
Population: Safety

Table 5.01
Summary of Demographic Characteristics

		Total (N=75)
Weight (kg)	n	75
	Mean	58.9
	SD	14.43
	Median	56.5
	Min.	34
	Max.	126
Body mass index (kg/m^2)	n	75
	Mean	22.7
	SD	4.74
	Median	21.8
	Min.	15
	Max.	47
Protocol ID	n	75
	BEL113750	3 (4%)
	BEL114333	1 (1%)
	HGS1006-C1056	4 (5%)
	HGS1006-C1057	14 (19%)
	HGS1006-C1066	4 (5%)
	HGS1006-C1070	4 (5%)
	HGS1006-C1074	30 (40%)
	HGS1006-C1115	3 (4%)
	LBSL02	6 (8%)
	LBSL99	6 (8%)

[redacted]

Protocol: 201182
Population: Safety

Table 5.02
Summary of Baseline Disease Characteristics

		Total (N=75)
Duration since diagnosis (y)	n	62
	Mean	4.4
	SD	3.86
	Median	3.4
	Min.	0
	Max.	17
Baseline Anti-dsDNA (IU/mL)	n	74
	Mean	137.3
	SD	242.27
	Median	73.5
	Min.	2
	Max.	1951
Baseline Anti-dsDNA >=30 IU/mL	n	74
	No	23 (31%)
	Yes	51 (69%)
Baseline ANA (Titer)	n	71
	Mean	801.7
	SD	529.24
	Median	1280.0
	Min.	9
	Max.	1281
Baseline C3 (Mg/dL)	n	75
	Mean	88.9
	SD	30.14
	Median	85.0
	Min.	31
	Max.	194

[redacted]

Table 5.02
Summary of Baseline Disease Characteristics

		Total (N=75)
Baseline C3 (Mg/dL) low	n	75
	No	31 (41%)
	Yes	44 (59%)
Baseline C4 (Mg/dL)	n	75
	Mean	14.7
	SD	8.08
	Median	14.0
	Min.	3
	Max.	38
Baseline C4 (Mg/dL) low	n	75
	No	35 (47%)
	Yes	40 (53%)
Baseline SLEDAI Score	n	75
	Mean	8.9
	SD	4.23
	Median	9.0
	Min.	0
	Max.	22
Baseline SLICC Index	n	59
	Mean	0.3
	SD	0.88
	Median	0.0
	Min.	0
	Max.	6

Protocol: 201182
Population: Safety

Table 5.02
Summary of Baseline Disease Characteristics

		Total (N=75)
Baseline PGA	n	74
	Mean	1.270
	SD	0.6439
	Median	1.31
	Min.	0.00
	Max.	2.58

[redacted]

Protocol: 201182
Population: Safety

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Any medical condition	67 (89%)
Musculoskeletal and connective tissue disorders	
Any medical condition	67 (89%)
Systemic lupus erythematosus	67 (89%)
SLE arthritis	29 (39%)
Arthralgia	21 (28%)
Myalgia	7 (9%)
Arthritis	4 (5%)
Osteopenia	4 (5%)
Synovitis	4 (5%)
Fibromyalgia	3 (4%)
Osteoporosis	3 (4%)
Pain in extremity	3 (4%)
Polyarthritis	3 (4%)
Back pain	2 (3%)
Joint swelling	2 (3%)
Musculoskeletal chest pain	2 (3%)
Musculoskeletal stiffness	2 (3%)
Scoliosis	2 (3%)
Sjogren's syndrome	2 (3%)
Tenosynovitis	2 (3%)
Bone disorder	1 (1%)
Flank pain	1 (1%)
Muscle spasms	1 (1%)
Muscular weakness	1 (1%)
Musculoskeletal pain	1 (1%)
Palindromic rheumatism	1 (1%)
Rheumatic disorder	1 (1%)
Spondylitis	1 (1%)
Tendonitis	1 (1%)
Trigger finger	1 (1%)

[redacted]

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Skin and subcutaneous tissue disorders	
Any medical condition	46 (61%)
Alopecia	34 (45%)
Butterfly rash	23 (31%)
Photosensitivity reaction	13 (17%)
Livedo reticularis	7 (9%)
Cutaneous lupus erythematosus	6 (8%)
Erythema	5 (7%)
Rash	4 (5%)
Ecchymosis	3 (4%)
Acne	2 (3%)
Cutaneous vasculitis	2 (3%)
Petechiae	2 (3%)
Pruritus	2 (3%)
Rash maculo-papular	2 (3%)
Skin mass	2 (3%)
Systemic lupus erythematosus rash	2 (3%)
Dermatitis atopic	1 (1%)
Hand dermatitis	1 (1%)
Hypersensitivity vasculitis	1 (1%)
Hypertrichosis	1 (1%)
Ingrowing nail	1 (1%)
Keloid scar	1 (1%)
Lividity	1 (1%)
Miliaria	1 (1%)
Palmar erythema	1 (1%)
Pigmentation disorder	1 (1%)
Purpura	1 (1%)
Seborrhoeic dermatitis	1 (1%)
Swelling face	1 (1%)
Telangiectasia	1 (1%)
Urticaria	1 (1%)

[redacted]

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Vascular disorders	
Any medical condition	37 (49%)
Raynaud's phenomenon	26 (35%)
Hypertension	14 (19%)
Vasculitis	5 (7%)
Deep vein thrombosis	2 (3%)
Lupus vasculitis	2 (3%)
Embolism venous	1 (1%)
Haemorrhage	1 (1%)
Lymphoedema	1 (1%)
Phlebolith	1 (1%)
Gastrointestinal disorders	
Any medical condition	35 (47%)
Mouth ulceration	15 (20%)
Gastritis	6 (8%)
Abdominal pain upper	5 (7%)
Nausea	5 (7%)
Constipation	4 (5%)
Diarrhoea	4 (5%)
Abdominal pain	3 (4%)
Dry mouth	3 (4%)
Gastrooesophageal reflux disease	2 (3%)
Gingival bleeding	2 (3%)
Pancreatitis	2 (3%)
Abdominal pain lower	1 (1%)
Ascites	1 (1%)
Buccal polyp	1 (1%)
Colitis	1 (1%)
Dental caries	1 (1%)
Dyspepsia	1 (1%)
Gastric ulcer	1 (1%)
Haemorrhoids	1 (1%)

[redacted]

Protocol: 201182
Population: Safety

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Hypoaesthesia oral	1 (1%)
Lip swelling	1 (1%)
Mouth haemorrhage	1 (1%)
Oesophagitis	1 (1%)
Parotid gland enlargement	1 (1%)
Salivary gland calculus	1 (1%)
Salivary gland cyst	1 (1%)
Vomiting	1 (1%)
Blood and lymphatic system disorders	
Any medical condition	28 (37%)
Anaemia	17 (23%)
Leukopenia	10 (13%)
Thrombocytopenia	8 (11%)
Antiphospholipid syndrome	7 (9%)
Lymphadenopathy	3 (4%)
Lymphopenia	3 (4%)
Increased tendency to bruise	2 (3%)
Neutropenia	2 (3%)
Pancytopenia	2 (3%)
Haemolytic anaemia	1 (1%)
Hypercoagulation	1 (1%)
Immune thrombocytopenic purpura	1 (1%)
Iron deficiency anaemia	1 (1%)
Leukocytosis	1 (1%)
Lymphadenitis	1 (1%)
Microcytosis	1 (1%)
Splenomegaly	1 (1%)
Thrombocytopenic purpura	1 (1%)
Thrombotic microangiopathy	1 (1%)
Infections and infestations	
Any medical condition	28 (37%)

[redacted]

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Herpes zoster	6 (8%)
Urinary tract infection	6 (8%)
Pneumonia	5 (7%)
Appendicitis	4 (5%)
Nasopharyngitis	4 (5%)
Upper respiratory tract infection	4 (5%)
Pyuria	3 (4%)
Bronchitis	2 (3%)
Fungal skin infection	2 (3%)
Onychomycosis	2 (3%)
Oral candidiasis	2 (3%)
Atypical pneumonia	1 (1%)
Carbuncle	1 (1%)
Cellulitis	1 (1%)
Cervicitis	1 (1%)
Cervicitis human papilloma virus	1 (1%)
Chest wall abscess	1 (1%)
Conjunctivitis	1 (1%)
Conjunctivitis viral	1 (1%)
Cystitis	1 (1%)
Folliculitis	1 (1%)
Herpes zoster cutaneous disseminated	1 (1%)
Herpes zoster oticus	1 (1%)
Meningitis aseptic	1 (1%)
Nocardiosis	1 (1%)
Ophthalmic herpes zoster	1 (1%)
Otitis media	1 (1%)
Pharyngitis	1 (1%)
Rash pustular	1 (1%)
Respiratory tract infection	1 (1%)
Salmonella sepsis	1 (1%)
Sepsis	1 (1%)
Skin infection	1 (1%)

[redacted]

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Tinea versicolour	1 (1%)
Urinary tract infection fungal	1 (1%)
Vaginal infection	1 (1%)
Vulvovaginitis	1 (1%)
Nervous system disorders	
Any medical condition	25 (33%)
Headache	11 (15%)
Migraine	9 (12%)
Dizziness	4 (5%)
Partial seizures	2 (3%)
Tremor	2 (3%)
VIIth nerve paralysis	2 (3%)
Amnesia	1 (1%)
Cerebral hypoperfusion	1 (1%)
Chorea	1 (1%)
Dysaesthesia	1 (1%)
Essential tremor	1 (1%)
Facial nerve disorder	1 (1%)
Lupus encephalitis	1 (1%)
Muscle contractions involuntary	1 (1%)
Neuralgia	1 (1%)
Neuropathy peripheral	1 (1%)
Post herpetic neuralgia	1 (1%)
Trigeminal neuralgia	1 (1%)
General disorders and administration site conditions	
Any medical condition	23 (31%)
Fatigue	15 (20%)
Pyrexia	8 (11%)
Non-cardiac chest pain	6 (8%)
Peripheral swelling	4 (5%)
Generalised oedema	3 (4%)

[redacted]

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Oedema peripheral	3 (4%)
Chest pain	2 (3%)
Chest discomfort	1 (1%)
Drug intolerance	1 (1%)
Face oedema	1 (1%)
Feeling cold	1 (1%)
Malaise	1 (1%)
Mucosal ulceration	1 (1%)
Nodule	1 (1%)
Pain	1 (1%)
Respiratory, thoracic and mediastinal disorders	
Any medical condition	23 (31%)
Dyspnoea	7 (9%)
Pleurisy	6 (8%)
Cough	3 (4%)
Epistaxis	3 (4%)
Nasal ulcer	3 (4%)
Pleural effusion	3 (4%)
Asthma	2 (3%)
Pleural fibrosis	2 (3%)
Pleuritic pain	2 (3%)
Rhinorrhoea	2 (3%)
Dysphonia	1 (1%)
Dyspnoea exertional	1 (1%)
Nasal congestion	1 (1%)
Nasal septum deviation	1 (1%)
Oropharyngeal pain	1 (1%)
Pharyngeal disorder	1 (1%)
Pneumonitis	1 (1%)
Pneumothorax	1 (1%)
Productive cough	1 (1%)
Pulmonary embolism	1 (1%)

[redacted]

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Pulmonary hypertension	1 (1%)
Pulmonary oedema	1 (1%)
Rhinitis allergic	1 (1%)
Vocal cord disorder	1 (1%)
Vocal cord inflammation	1 (1%)
Vocal cord thickening	1 (1%)
Renal and urinary disorders	
Any medical condition	22 (29%)
Lupus nephritis	10 (13%)
Proteinuria	6 (8%)
Glomerulonephritis	4 (5%)
Haematuria	3 (4%)
Nephrolithiasis	2 (3%)
Calculus urinary	1 (1%)
Glomerulonephritis membranoproliferative	1 (1%)
Mesangioproliferative glomerulonephritis	1 (1%)
Nephropathy	1 (1%)
Nephrotic syndrome	1 (1%)
Investigations	
Any medical condition	20 (27%)
Biopsy kidney	8 (11%)
Antinuclear antibody positive	7 (9%)
DNA antibody positive	5 (7%)
Complement factor decreased	3 (4%)
Activated partial thromboplastin time prolonged	2 (3%)
Alanine aminotransferase increased	2 (3%)
Antinuclear antibody increased	2 (3%)
Aspartate aminotransferase increased	2 (3%)
Cardiolipin antibody positive	2 (3%)
Complement factor C3 decreased	2 (3%)
Antiphospholipid antibodies positive	1 (1%)

[redacted]

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Aspiration pleural cavity	1 (1%)
Biopsy bone marrow normal	1 (1%)
Biopsy liver	1 (1%)
Biopsy lymph gland	1 (1%)
Biopsy skin	1 (1%)
Biopsy soft tissue	1 (1%)
Cardiac murmur	1 (1%)
Cardiac murmur functional	1 (1%)
Complement factor C4 decreased	1 (1%)
DNA antibody negative	1 (1%)
Double stranded DNA antibody positive	1 (1%)
Platelet count decreased	1 (1%)
Protein total decreased	1 (1%)
Prothrombin time prolonged	1 (1%)
Smear cervix normal	1 (1%)
Tuberculin test positive	1 (1%)
Urinary casts	1 (1%)
Urinary sediment present	1 (1%)
Urine analysis abnormal	1 (1%)
Weight decreased	1 (1%)
Surgical and medical procedures	
Any medical condition	18 (24%)
Appendicectomy	4 (5%)
Caesarean section	4 (5%)
Cholecystectomy	4 (5%)
Ovarian cystectomy	2 (3%)
Pericardial excision	2 (3%)
Abortion induced	1 (1%)
Cervical conisation	1 (1%)
Cyst removal	1 (1%)
Eventration repair	1 (1%)
Haemorrhoid operation	1 (1%)

[redacted]

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Limb operation	1 (1%)
Loop electrosurgical excision procedure	1 (1%)
Lymphadenectomy	1 (1%)
Oral polypectomy	1 (1%)
Pericardial drainage	1 (1%)
Cardiac disorders	
Any medical condition	16 (21%)
Pericardial effusion	5 (7%)
Palpitations	3 (4%)
Tachycardia	3 (4%)
Cyanosis	2 (3%)
Mitral valve incompetence	2 (3%)
Arteritis coronary	1 (1%)
Cardiac tamponade	1 (1%)
Cardiomegaly	1 (1%)
Coronary artery disease	1 (1%)
Diastolic dysfunction	1 (1%)
Left ventricular hypertrophy	1 (1%)
Mitral valve prolapse	1 (1%)
Pericarditis	1 (1%)
Pericarditis lupus	1 (1%)
Pleuropericarditis	1 (1%)
Sinus tachycardia	1 (1%)
Tricuspid valve incompetence	1 (1%)
Reproductive system and breast disorders	
Any medical condition	13 (17%)
Ovarian cyst	3 (4%)
Cervical dysplasia	2 (3%)
Adenomyosis	1 (1%)
Amenorrhoea	1 (1%)
Dysmenorrhoea	1 (1%)

[redacted]

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Endometriosis	1 (1%)
Fibrocystic breast disease	1 (1%)
Galactorrhoea	1 (1%)
Menometrorrhagia	1 (1%)
Menstruation irregular	1 (1%)
Metrorrhagia	1 (1%)
Uterine cervical squamous metaplasia	1 (1%)
Vaginal discharge	1 (1%)
Eye disorders	
Any medical condition	12 (16%)
Cataract	3 (4%)
Dry eye	3 (4%)
Eyelid oedema	2 (3%)
Conjunctival haemorrhage	1 (1%)
Erythema of eyelid	1 (1%)
Eye pruritus	1 (1%)
Eyelid pain	1 (1%)
Macular oedema	1 (1%)
Photophobia	1 (1%)
Pupils unequal	1 (1%)
Retinal artery occlusion	1 (1%)
Retinal exudates	1 (1%)
Retinal oedema	1 (1%)
Retinopathy	1 (1%)
Ulcerative keratitis	1 (1%)
Vision blurred	1 (1%)
Endocrine disorders	
Any medical condition	10 (13%)
Cushingoid	5 (7%)
Hypothyroidism	2 (3%)
Cushing's syndrome	1 (1%)

[redacted]

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Primary hypogonadism	1 (1%)
Thyroiditis	1 (1%)
Psychiatric disorders	
Any medical condition	10 (13%)
Depression	6 (8%)
Anxiety	3 (4%)
Insomnia	3 (4%)
Agoraphobia	1 (1%)
Mood swings	1 (1%)
Neurosis	1 (1%)
Panic attack	1 (1%)
Sleep disorder	1 (1%)
Hepatobiliary disorders	
Any medical condition	9 (12%)
Cholelithiasis	3 (4%)
Autoimmune hepatitis	1 (1%)
Cholecystitis	1 (1%)
Gallbladder polyp	1 (1%)
Hepatitis acute	1 (1%)
Hepatitis toxic	1 (1%)
Hepatomegaly	1 (1%)
Lupus hepatitis	1 (1%)
Pregnancy, puerperium and perinatal conditions	
Any medical condition	8 (11%)
Abortion spontaneous	5 (7%)
Pre-eclampsia	3 (4%)
HELLP syndrome	1 (1%)
Habitual abortion	1 (1%)
Multiple pregnancy	1 (1%)
Premature baby	1 (1%)

[redacted]

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Immune system disorders	
Any medical condition	6 (8%)
Drug hypersensitivity	4 (5%)
Seasonal allergy	2 (3%)
Allergy to metals	1 (1%)
Injury, poisoning and procedural complications	
Any medical condition	6 (8%)
Contusion	1 (1%)
Frostbite	1 (1%)
Joint dislocation	1 (1%)
Rib fracture	1 (1%)
Scar	1 (1%)
Spinal compression fracture	1 (1%)
Wound evisceration	1 (1%)
Metabolism and nutrition disorders	
Any medical condition	6 (8%)
Decreased appetite	3 (4%)
Hypoalbuminaemia	3 (4%)
Dyslipidaemia	1 (1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Any medical condition	3 (4%)
Anogenital warts	1 (1%)
Chondroma	1 (1%)
Vulvovaginal warts	1 (1%)
Congenital, familial and genetic disorders	
Any medical condition	1 (1%)
Congenital uterine anomaly	1 (1%)

[redacted]

Protocol: 201182
Population: Safety

Table 5.03
Summary of Baseline Medical History

System Organ Class Preferred Term	Total (N=75)
Ear and labyrinth disorders	
Any medical condition	1 (1%)
Tinnitus	1 (1%)
Social circumstances	
Any medical condition	1 (1%)
Tobacco user	1 (1%)

[redacted]

Protocol: 201182
Population: Safety

Table 5.04
Summary of Concomitant Medications

ATC Level 1 Ingredient(s)	Total (N=75)
Any medication	44 (59%)
ALIMENTARY TRACT AND METABOLISM	
Any medication	23 (31%)
OMEPRAZOLE	8 (11%)
PREDNISONE	7 (9%)
CALCIUM	6 (8%)
CALCIUM CARBONATE	3 (4%)
COLECALCIFEROL	3 (4%)
Multiple Ingredient	3 (4%)
LANSOPRAZOLE	2 (3%)
VITAMIN D NOS	2 (3%)
VITAMINS NOS	2 (3%)
ACETYLSALICYLIC ACID	1 (1%)
ALFACALCIDOL	1 (1%)
ASCORBIC ACID	1 (1%)
CALTRATE 600 + D	1 (1%)
CHLOROQUINE	1 (1%)
DICYCLOVERINE HYDROCHLORIDE	1 (1%)
FAMOTIDINE	1 (1%)
METOCLOPRAMIDE	1 (1%)
MINERALS NOS	1 (1%)
MISOPROSTOL	1 (1%)
ONDANSETRON	1 (1%)
PANTOPRAZOLE	1 (1%)
POTASSIUM NOS	1 (1%)
PRENATAL VITAMINS	1 (1%)
PROMETHAZINE HYDROCHLORIDE	1 (1%)
REBAMIPIDE	1 (1%)
TOCOPHEROL	1 (1%)
TRIAMCINOLONE ACETONIDE	1 (1%)
VITAMIN COMPLEX (NOS)	1 (1%)
VITAMIN D	1 (1%)

[redacted]

Table 5.04
Summary of Concomitant Medications

ATC Level 1 Ingredient(s)	Total (N=75)
VITAMIN D3	1 (1%)
NERVOUS SYSTEM	
Any medication	23 (31%)
PARACETAMOL	8 (11%)
ACETAMINOPHEN	5 (7%)
ACETYLSALICYLIC ACID	3 (4%)
DIAZEPAM	2 (3%)
LORAZEPAM	2 (3%)
BUTALBITAL, ACETAMINOPHEN & CAFFEINE	1 (1%)
CITALOPRAM	1 (1%)
CLONAZEPAM	1 (1%)
DEXTROMETHORPHAN HBR W/DOXYLAM. SUCC/PARACET.	1 (1%)
GABAPENTIN	1 (1%)
HYDROCODONE	1 (1%)
HYDROCODONE BITARTRATE	1 (1%)
LEVOMEPROMAZINE	1 (1%)
METAMIZOLE SODIUM	1 (1%)
NALBUPHINE HYDROCHLORIDE	1 (1%)
PAROXETINE	1 (1%)
PREGABALIN	1 (1%)
THERAFLU	1 (1%)
TOPIRAMATE	1 (1%)
TRAMADOL	1 (1%)
TYLENOL COLD SEVERE CONGESTION	1 (1%)
VALPROIC ACID	1 (1%)
ZOLPIDEM	1 (1%)
ZOLPIDEM TARTRATE	1 (1%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	
Any medication	21 (28%)
PREDNISONE	9 (12%)

[redacted]

Table 5.04
Summary of Concomitant Medications

ATC Level 1 Ingredient(s)	Total (N=75)
METHYLPREDNISOLONE	6 (8%)
PREDNISOLONE	6 (8%)
HYDROCORTISONE	3 (4%)
LEVOTHYROXINE SODIUM	2 (3%)
BETAMETHASONE	1 (1%)
DEXAMETHASONE	1 (1%)
LEVOTHYROXINE	1 (1%)
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	
Any medication	19 (25%)
HYDROXYCHLOROQUINE	12 (16%)
CHLOROQUINE	7 (9%)
DERMATOLOGICALS	
Any medication	19 (25%)
ACETAMINOPHEN	11 (15%)
AMOXICILLIN	6 (8%)
DIPHENHYDRAMINE	6 (8%)
HYDROXYCHLOROQUINE	6 (8%)
PRENATAL VITAMINS	6 (8%)
CALCIUM	5 (7%)
CIPROFLOXACIN	5 (7%)
METHYLPREDNISOLONE	5 (7%)
PREDNISONE	5 (7%)
FOLIC ACID	4 (5%)
LEVOFLOXACIN	4 (5%)
MYCOPHENOLATE MOFETIL	4 (5%)
VITAMIN D	4 (5%)
ACETAMINOPHEN W/HYDROCODONE BITARTRATE	3 (4%)
ALBUTEROL	3 (4%)
ALENDRONATE SODIUM	3 (4%)
AZITHROMYCIN	3 (4%)
CALCIUM CARBONATE	3 (4%)

[redacted]

Table 5.04
Summary of Concomitant Medications

ATC Level 1 Ingredient(s)	Total (N=75)	
IBUPROFEN	3	(4%)
LISINOPRIL	3	(4%)
NORMAL SALINE	3	(4%)
PROMETHAZINE HYDROCHLORIDE	3	(4%)
ACETAMINOPHEN W/CODEINE	2	(3%)
AMOXICILLIN W/CLAVULANATE POTASSIUM	2	(3%)
CYCLOBENZAPRINE HYDROCHLORIDE	2	(3%)
DIPHENHYDRAMINE HYDROCHLORIDE	2	(3%)
DOCUSATE SODIUM	2	(3%)
DOXYCYCLINE	2	(3%)
GUAIFENESIN	2	(3%)
HYDROCHLOROTHIAZIDE	2	(3%)
INFLUENZA VACCINE	2	(3%)
LANSOPRAZOLE	2	(3%)
LORAZEPAM	2	(3%)
MEPACRINE HYDROCHLORIDE	2	(3%)
MEPERIDINE HYDROCHLORIDE	2	(3%)
METHYLPREDNISOLONE SODIUM SUCCINATE	2	(3%)
METRONIDAZOLE	2	(3%)
NITROFURANTOIN	2	(3%)
NYSTATIN	2	(3%)
OMEPRAZOLE	2	(3%)
OSELTAMIVIR PHOSPHATE	2	(3%)
PROCHLORPERAZINE	2	(3%)
PROMETHAZINE	2	(3%)
SODIUM CITRATE	2	(3%)
TRAZODONE	2	(3%)
TRIAMCINOLONE	2	(3%)
VALACICLOVIR	2	(3%)
VALACICLOVIR HYDROCHLORIDE	2	(3%)
VITAMIN E	2	(3%)
ZINC OXIDE	2	(3%)
ZOLPIDEM TARTRATE	2	(3%)

[redacted]

Table 5.04
Summary of Concomitant Medications

ATC Level 1 Ingredient(s)	Total (N=75)
ACETYLSALICYLIC ACID	1 (1%)
ACICLOVIR	1 (1%)
ALKA-SELTZER PLUS COLD & COUGH	1 (1%)
ALPRAZOLAM	1 (1%)
AMLODIPINE	1 (1%)
AMLODIPINE BESILATE	1 (1%)
AZATHIOPRINE	1 (1%)
BACITRACIN	1 (1%)
BENAZEPRIL	1 (1%)
BENTONITE	1 (1%)
BISACODYL	1 (1%)
BUDESONIDE W/FORMOTEROL FUMARATE	1 (1%)
CALAMINE	1 (1%)
CANDIDA ALBICANS SKIN TEST ANTIGEN	1 (1%)
CARISOPRODOL	1 (1%)
CEFTRIAXONE	1 (1%)
CENTRUM	1 (1%)
CEPHALEXIN	1 (1%)
CETIRIZINE	1 (1%)
CIMETIDINE	1 (1%)
CLINDAMYCIN	1 (1%)
CLOBETASOL	1 (1%)
COD-LIVER OIL	1 (1%)
CYCLOBENZAPRINE	1 (1%)
DESLORATADINE	1 (1%)
DEXTROMETHORPHAN HYDROBROMIDE W/GUAIFENESIN	1 (1%)
DICLOXACILLIN SODIUM	1 (1%)
DIMENHYDRINATE	1 (1%)
DULOXETINE	1 (1%)
ESOMEPRAZOLE MAGNESIUM	1 (1%)
FAMCICLOVIR	1 (1%)
FERROUS GLUCONATE	1 (1%)
FERROUS SULFATE	1 (1%)

[redacted]

Table 5.04
Summary of Concomitant Medications

ATC Level 1 Ingredient(s)	Total (N=75)
FISH OIL	1 (1%)
FLAXSEED OIL	1 (1%)
FLUCONAZOLE	1 (1%)
FLUOXETINE	1 (1%)
FLUTICASONE PROPIONATE W/SALMETEROL XINAFOATE	1 (1%)
FUROSEMIDE	1 (1%)
GATIFLOXACIN	1 (1%)
GLYCEROL	1 (1%)
HYDROCODONE BITARTRATE W/IBUPROFEN	1 (1%)
HYDROCORTISONE	1 (1%)
HYDROMORPHONE	1 (1%)
IRON	1 (1%)
KETOROLAC TROMETHAMINE	1 (1%)
LEUCOVORIN	1 (1%)
LEVOTHYROXINE	1 (1%)
LIDOCAINE	1 (1%)
LISINOPRIL W/HYDROCHLOROTHIAZIDE	1 (1%)
LORATADINE	1 (1%)
MEDROXYPROGESTERONE	1 (1%)
MOMETASONE FUROATE	1 (1%)
MORPHINE SULFATE	1 (1%)
MOXIFLOXACIN	1 (1%)
MULTIVITAMINS PLUS IRON	1 (1%)
MULTIVITAMINS, PLAIN	1 (1%)
NAPROXEN	1 (1%)
NIFEDIPINE	1 (1%)
NOR-QD	1 (1%)
NUVA RING	1 (1%)
NYQUIL	1 (1%)
ONDANSETRON HYDROCHLORIDE	1 (1%)
ORTHO TRI-CYCLEN	1 (1%)
PAROXETINE	1 (1%)
PENICILLIN	1 (1%)

[redacted]

Table 5.04
Summary of Concomitant Medications

ATC Level 1 Ingredient(s)	Total (N=75)
PHENAZOPYRIDINE	1 (1%)
PHENOL, LIQUEFIED	1 (1%)
PIROXICAM	1 (1%)
PNEUMOCOCCAL VACCINE	1 (1%)
POTASSIUM CHLORIDE	1 (1%)
PROCHLORPERAZINE MALEATE	1 (1%)
PSEUDOEPHEDRINE HYDROCHLORIDE	1 (1%)
QUINAPRIL HYDROCHLORIDE	1 (1%)
RANITIDINE	1 (1%)
RHOGAM	1 (1%)
SALICYLIC ACID	1 (1%)
SELENIUM SULFIDE	1 (1%)
SENNA	1 (1%)
SERTRALINE	1 (1%)
SERTRALINE HYDROCHLORIDE	1 (1%)
STOMATOLOGICALS, MOUTH PREPARATIONS	1 (1%)
SUCRALFATE	1 (1%)
SUDAFED	1 (1%)
SULFAMETHOXAZOLE W/TRIMETHOPRIM	1 (1%)
SUNSCREEN	1 (1%)
TRETINOIN	1 (1%)
TYLENOL COLD	1 (1%)
TYLENOL COLD & FLU	1 (1%)
TYLENOL SINUS	1 (1%)
VARENICLINE	1 (1%)
VITAMIN C	1 (1%)
ZOLPIDEM	1 (1%)
MUSCULO-SKELETAL SYSTEM	
Any medication	19 (25%)
HYDROXYCHLOROQUINE	5 (7%)
NAPROXEN	5 (7%)
DICLOFENAC	3 (4%)

[redacted]

Table 5.04
Summary of Concomitant Medications

ATC Level 1 Ingredient(s)	Total (N=75)
IBUPROFEN	2 (3%)
MELOXICAM	2 (3%)
ACECLOFENAC	1 (1%)
ACEMETACIN	1 (1%)
ALENDRONATE SODIUM	1 (1%)
HYDROXYCHLOROQUINE SULFATE	1 (1%)
INDOMETACIN	1 (1%)
PIROXICAM	1 (1%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	
Any medication	14 (19%)
AZATHIOPRINE	8 (11%)
METHOTREXATE	2 (3%)
CYCLOPHOSPHAMIDE	1 (1%)
MIZORIBINE	1 (1%)
MYCOPHENOLATE MOFETIL	1 (1%)
THALIDOMIDE	1 (1%)
CARDIOVASCULAR SYSTEM	
Any medication	14 (19%)
ENALAPRIL	3 (4%)
FUROSEMIDE	2 (3%)
HYDROCHLOROTHIAZIDE	2 (3%)
LISINOPRIL	2 (3%)
NIFEDIPINE	2 (3%)
SIMVASTATIN	2 (3%)
AMBRISENTAN	1 (1%)
AMILORIDE HYDROCHLORIDE	1 (1%)
AMLODIPINE	1 (1%)
ASPARTATE POTASSIUM W/MAGNESIUM ASPARTATE	1 (1%)
ATENOLOL	1 (1%)
BENCYCLANE FUMARATE	1 (1%)
FELODIPINE	1 (1%)

[redacted]

Table 5.04
Summary of Concomitant Medications

ATC Level 1 Ingredient(s)	Total (N=75)
FISH OIL	1 (1%)
LOSARTAN	1 (1%)
PENTOXIFYLLINE	1 (1%)
SILDENAFIL CITRATE	1 (1%)
VALSARTAN	1 (1%)
ANTIINFECTIVES FOR SYSTEMIC USE	
Any medication	12 (16%)
AZITHROMYCIN	3 (4%)
CEFALEXIN	2 (3%)
CIPROFLOXACIN	2 (3%)
NORFLOXACIN	2 (3%)
AMOXICILLIN W/CLAVULANIC ACID	1 (1%)
AMPICILLIN W/SULBACTAM	1 (1%)
CLARITHROMYCIN	1 (1%)
DICLOXACILLIN	1 (1%)
DOXYCYCLINE	1 (1%)
FLUCONAZOLE	1 (1%)
INFLUENZA VACCINE	1 (1%)
INFLUENZA VIRUS VACCINE INACTIVATED	1 (1%)
OSELTAMIVIR PHOSPHATE	1 (1%)
GENITO URINARY SYSTEM AND SEX HORMONES	
Any medication	11 (15%)
MISOPROSTOL	2 (3%)
BENZALKONIUM CHLORIDE	1 (1%)
CLOTRIMAZOLE	1 (1%)
DROSPIRENONE W/ETHINYLESTRADIOL	1 (1%)
DYDROGESTERONE	1 (1%)
ETHINYLESTRADIOL W/GESTODENE	1 (1%)
FURADONINE	1 (1%)
IBUPROFEN	1 (1%)
LOESTRIN	1 (1%)

[redacted]

Table 5.04
Summary of Concomitant Medications

ATC Level 1 Ingredient(s)	Total (N=75)
METHYLERGOMETRINE MALEATE	1 (1%)
MIFEPRISTONE	1 (1%)
NAPROXEN	1 (1%)
BLOOD AND BLOOD FORMING ORGANS	
Any medication	8 (11%)
ACETYLSALICYLIC ACID	4 (5%)
ENOXAPARIN	2 (3%)
ACENOCOUMAROL	1 (1%)
FERRIC HYDROXIDE POLYMALTOSE COMPLEX	1 (1%)
FOLIC ACID	1 (1%)
IRON	1 (1%)
SULODEXIDE	1 (1%)
VITAMIN B12	1 (1%)
VITAMIN K	1 (1%)
RESPIRATORY SYSTEM	
Any medication	6 (8%)
LORATADINE	3 (4%)
BENPROPERINE	1 (1%)
CHLOROPYRAMINE	1 (1%)
DIPHENHYDRAMINE	1 (1%)
DIPHENHYDRAMINE HYDROCHLORIDE	1 (1%)
FEXOFENADINE	1 (1%)
FEXOFENADINE HYDROCHLORIDE	1 (1%)
VARIOUS	
Any medication	3 (4%)
PAEONIA EXTRACT (NOS)	2 (3%)
FOLIC ACID	1 (1%)
Multiple Ingredient	1 (1%)

[redacted]

Protocol: 201182
Population: Safety

Table 5.05
Summary of Infections

System Organ Class Preferred Term	Total (N=75)
Any event	39 (52%)
Infections and infestations	
Any event	39 (52%)
Influenza	9 (12%)
Nasopharyngitis	8 (11%)
Upper respiratory tract infection	6 (8%)
Cystitis	4 (5%)
Gastroenteritis	4 (5%)
Viral upper respiratory tract infection	4 (5%)
Bronchitis	3 (4%)
Urinary tract infection bacterial	3 (4%)
Cellulitis	2 (3%)
Pharyngitis	2 (3%)
Upper respiratory tract infection bacterial	2 (3%)
Urinary tract infection	2 (3%)
Vulvovaginal candidiasis	2 (3%)
Appendicitis	1 (1%)
Asymptomatic bacteriuria	1 (1%)
Bacterial vaginosis	1 (1%)
Body tinea	1 (1%)
Bronchitis viral	1 (1%)
Conjunctivitis	1 (1%)
Cystitis bacterial	1 (1%)
Cytomegalovirus infection	1 (1%)
Escherichia urinary tract infection	1 (1%)
Furuncle	1 (1%)
Gastritis viral	1 (1%)
Genital herpes	1 (1%)
Gingivitis	1 (1%)
Gonorrhoea	1 (1%)
H1N1 influenza	1 (1%)
Herpes zoster	1 (1%)

[redacted]

Protocol: 201182
Population: Safety

Table 5.05
Summary of Infections

System Organ Class Preferred Term	Total (N=75)
Laryngitis	1 (1%)
Oral candidiasis	1 (1%)
Otitis media	1 (1%)
Pelvic inflammatory disease	1 (1%)
Periodontitis	1 (1%)
Pharyngitis bacterial	1 (1%)
Pneumonia	1 (1%)
Pyelonephritis acute	1 (1%)
Pyoderma	1 (1%)
Pyuria	1 (1%)
Sialoadenitis	1 (1%)
Sinusitis	1 (1%)
Skin bacterial infection	1 (1%)
Skin infection	1 (1%)
Tooth abscess	1 (1%)
Tooth infection	1 (1%)
Vaginal infection	1 (1%)
Viral pharyngitis	1 (1%)
Viral rhinitis	1 (1%)
Viral sinusitis	1 (1%)
Vulvovaginal mycotic infection	1 (1%)
Vulvovaginitis	1 (1%)

Protocol: 201182
Population: Safety

Table 5.06
Summary of Disease Characteristics Prior to Pregnancy Reference Date

		Total (N=75)
Duration since diagnosis (y)	n	62
	Mean	4.4
	SD	3.86
	Median	3.4
	Min.	0
	Max.	17
Anti-dsDNA (IU/mL)	n	41
	Mean	101.0
	SD	109.24
	Median	71.0
	Min.	3
	Max.	608
Anti-dsDNA >=30 IU/mL	n	41
	No	16 (39%)
	Yes	25 (61%)
ANA (Titer)	n	37
	Mean	703.1
	SD	560.61
	Median	640.0
	Min.	39
	Max.	1281
C3 (Mg/dL)	n	41
	Mean	97.2
	SD	30.56
	Median	98.0
	Min.	39
	Max.	194

[redacted]

Table 5.06
Summary of Disease Characteristics Prior to Pregnancy Reference Date

		Total (N=75)
C3 (Mg/dL) low	n	41
	No	24 (59%)
	Yes	17 (41%)
C4 (Mg/dL)	n	41
	Mean	17.8
	SD	9.37
	Median	18.0
	Min.	3
	Max.	38
C4 (Mg/dL) low	n	41
	No	23 (56%)
	Yes	18 (44%)
SLEDAI Total Score	n	73
	Mean	5.5
	SD	3.72
	Median	4.0
	Min.	0
	Max.	21
SLICC Damage Index	n	30
	Mean	0.6
	SD	1.19
	Median	0.0
	Min.	0
	Max.	6

[redacted]

Protocol: 201182
Population: Safety

Table 5.06
Summary of Disease Characteristics Prior to Pregnancy Reference Date

		Total (N=75)
PGA	n	37
	Mean	1.424
	SD	1.2372
	Median	1.02
	Min.	0.00
	Max.	5.90

[redacted]

Protocol: 201182
Population: Safety

Table 5.07
Summary of Demographic Characteristics for Placebo Subjects

		Total (N=8)
Age at screening (y)	n	8
	Mean	29.9
	SD	6.38
	Median	30.0
	Min.	20
	Max.	38
Age at delivery (y)	n	8
	Mean	31.0
	SD	6.32
	Median	31.5
	Min.	21
	Max.	40
Age Group 1 at delivery	n	8
	20-24 Years	1 (13%)
	25-29 Years	2 (25%)
	30-34 Years	3 (38%)
	35-39 Years	1 (13%)
	40-44 Years	1 (13%)
Age Group 2 at delivery	n	8
	<35 Years	6 (75%)
	>=35 Years	2 (25%)
Race	n	8
	White	2 (25%)
	Black or African American	1 (13%)
	Asian	3 (38%)
	Alaska Native or American Indian	2 (25%)

[redacted]

Protocol: 201182
Population: Safety

Table 5.07
Summary of Demographic Characteristics for Placebo Subjects

		Total (N=8)
Ethnicity	n	8
	Hispanic or Latino	3 (38%)
	Not Hispanic or Latino	5 (63%)
Country	n	8
	Brazil	1 (13%)
	China	2 (25%)
	Peru	2 (25%)
	Philippines	1 (13%)
	Romania	1 (13%)
	United States	1 (13%)
Height (cm)	n	8
	Mean	156.6
	SD	3.74
	Median	157.3
	Min.	151
	Max.	162
Weight (kg)	n	8
	Mean	58.3
	SD	9.41
	Median	58.2
	Min.	46
	Max.	72
Body mass index (kg/m^2)	n	8
	Mean	23.8
	SD	4.14
	Median	24.1
	Min.	18
	Max.	30

[redacted]

Protocol: 201182
Population: Safety

Table 5.07
Summary of Demographic Characteristics for Placebo Subjects

		Total (N=8)
Protocol ID	n	8
	BEL113750	2 (25%)
	HGS1006-C1057	5 (63%)
	LBSL02	1 (13%)

[redacted]

Synopsis

Name of company: GlaxoSmithKline Research & Development Limited

Name of finished product: Benlysta **Name of active substance:** Belimumab

Study Number: 201182

Title: Meta-Analysis Results Report for Study Number 201182, GSK1550188, SLE, Pregnancy Analysis

Publication(s):

None at the time of this report.

Study Period: Start of intravenous (IV) systemic lupus erythematosus (SLE) Phase 2 clinical trials up to 08MAR2014

Phase of Development: II – IV pooled study data

Objectives: The primary objective is to determine if there is an increase in birth defects in infants born to women with SLE who were exposed to belimumab during pregnancy. A full listing of trials appears in List of clinical trials included in aggregate analysis.

Secondary outcomes include adverse maternal and infant outcomes, e.g. spontaneous miscarriage, preterm birth and still birth. Another secondary objective of these analyses was to evaluate concomitant medication use prior to pregnancy.

Methodology: All pregnancies reported in belimumab clinical trials were identified in the GSK Safety Reporting Database. The search is based on the SMQ Pregnancy and Neonatal Topics. In addition, all cases involving a pregnant patient are included. Cases involving females over 60 years of age and adult males (where the case was not reported as a partner pregnancy) have been excluded. The primary analytical population includes all unblinded subjects who had a pregnancy identified with a known outcome while participating in a belimumab clinical trial. Eligibility for the Phase 3 clinical trials (largest contributor of subjects to the clinical trial were in a continuation trial of one of the parent Phase 3 studies) included adult subjects on background therapy with active SLE disease, defined as a SELENA-SLEDAI score ≥ 6 and positive ANA (ANA titer ≥ 1:80) and/or anti-dsDNA (≥ 30 IU/mL) test results at screening.

Key variables included pregnancy outcomes, estimated date of delivery, disease activity, laboratory data, and each data variable was derived from the clinical trial database and/or the GSK safety database for the purpose of evaluating maternal, fetal and infant outcome data for subjects with systemic lupus erythematosus (SLE) who were exposed to belimumab during pregnancy. Timing of exposure was calculated by adding 100 days (five elimination half-lives of belimumab) to the last belimumab dose.

Number of subjects:

All pregnancies with an unblinded treatment assignment prior to the 08 March, 2014 data lock point reported in belimumab SLE clinical trials up to 08 March 2014.

Diagnosis and main criteria for inclusion: Women in belimumab SLE clinical trials (Phase II-IV) who received study drug four months prior to conception and/or during an identified pregnancy.

Treatment administration: Subjects participating in blinded studies were administered either belimumab (intravenous (IV) or subcutaneous (SC)) or placebo in addition to standard care. Subjects participating in open-label or observational post marketing studies all received belimumab (IV or SC). Primary treatment comparison across exposure groups (1mg/kg IV, 4mg/kg IV, 10mg/kg IV, SC, or placebo) is based on the last dose received prior to or during pregnancy.

Criteria for evaluation:

All pregnancies with an unblinded treatment assignment prior to the 08 March, 2014 data lock point reported in belimumab SLE clinical trials up to 08 March 2014. Demographic and baseline characteristics also include pregnancies that were lost to follow-up (LTF).

Statistical methods:

All data are summarized using descriptive statistics. Continuous variables are summarized by number of participants, mean, standard deviation (SD), median, lower quartile, upper quartile, minimum and maximum unless otherwise stated. Categorical variables are summarized by number and percentage in each category. Missing data are displayed as a separate category where appropriate. The denominator for all percentages will reflect the number of participants within the cohort, unless otherwise stated (e.g. excluding lost to follow-up (LTF)). All data analyses and reporting were performed using SAS Version 9.3.

For primary endpoint (birth defects) and secondary endpoints (pregnancy outcomes: live birth, neonatal death, stillbirth, spontaneous miscarriage, elective termination, ectopic pregnancy, and molar pregnancy) prevalence rates and 95% confidence intervals are summarized. Confidence intervals for birth defect prevalence will be calculated under the exact binomial distribution assumption. Results will also be stratified by timing of exposure and subgroup.

Birth defects will be classified as known chromosomal or syndromic, or specific organ system defect (e.g. cardiovascular, musculoskeletal to include limb defects, urogenital, neural tube defects, gastrointestinal, and other structural defects (including cleft lip and cleft palate)). The prevalence of birth defects will be calculated as the percentage of total birth defects and by organ system from the total number of live births in the study population and then also stratified by subgroup. Fetal losses with reported birth defects occurring at or after 20 weeks gestation will be included in the numerator of the estimate of risk for birth defects to increase sensitivity.

Each pregnancy outcome is defined as one of the following: live birth, neonatal death, stillbirth, spontaneous miscarriage, elective termination, ectopic pregnancy, and molar pregnancy. Prevalence rates and 95% confidence intervals will be computed for the primary and secondary objectives.

All pregnancy outcomes are summarized by the following subgroups:

- Maternal Age
- Region
- PGA Score (≥2)
- SDI (>1)
- Concomitant Medications and Pregnancy Drug Category D or X

Results are also presented by timing of belimumab exposure for the overall summaries and within each subgroup.

Summary:

Of the 38 live births, four birth defects were reported, two of which had belimumab exposure through the first trimester and two through the second trimester. All of these defects were in women <35 years of age at conception. Of these four birth defects, one patient was in the 1 mg/kg treatment group and the three others were taking 10 mg/kg. Two of these subjects had a PGA ≥2 at the most recent disease activity assessment prior to pregnancy. Birth defects were also broken down by organ system. Of the four birth defects, one was chromosomal, one was cardiovascular, one was urogenital and one was a neural tube defect

A secondary objective of these analyses was to evaluate concomitant medication use prior to pregnancy. Three of the 4 reported pregnancies with a birth defect occurred in patients taking a steroid and anti-malarial, one taking a steroid, anti-malarial and immunosuppressant and one taking a category D or X drug (ambrisentan).

Of the 77 pregnancies with known outcomes included in the analyses, there were 38 (49%) live births (20 full-term and 18 preterm), one (1%) stillbirth, 19 (25%) spontaneous miscarriages and 19 (25%) elective terminations. The belimumab dose for 32 of the live births was 10mg/kg. Of the 38 live births, six subjects were taking a steroid, one subject was taking an immunosuppressant, 11 subjects were taking a steroid and antimalarial, four subjects were taking a steroid and immunosuppressant, one subject was taking an immunosuppressant and antimalarial, 13 subjects were taking an antimalarial, steroid, and immunosuppressant. Sixteen subjects were taking a category D or X drugs prior/during pregnancy.

Conclusions:

The frequency of fetal loss including spontaneous miscarriage and stillbirths is consistent with ranges cited in a recent review of pregnancy outcomes in SLE. This review of 45 studies cited the range of fetal death from 4% to 43%. The authors commented, “Fetal

prognosis corresponds with disease activity, with fetal loss ranging from 25-52% in patients with active SLE compared to 8-12% in patients with inactive SLE at the onset of pregnancy. The latter rate is comparable to observations in healthy women."

At this time, the total number of live births with known outcomes is not sufficient to make quantitative comparisons of the prevalence of birth defects relative to another SLE population or the general population. The cases were reviewed in terms of embryological or biological considerations: The case of unbalanced translocation of chromosome 11/13 is not attributed to belimumab because it is not expected that a monoclonal IgG antibody would interact with DNA or chromosomal material. The three remaining birth defect cases, Dandy Walker Syndrome, renal failure, and pulmonary stenosis are each unique reports.

Effective Date: 16-NOV-2015

Division: Worldwide Development
Retention Category: GRS019
Information Type: Meta-Analysis Plan

Title:	Meta-Analysis Plan for Study Number 201182, GSK1550188, SLE, Pregnancy Analysis

Compound Number: GSK1550188

Effective Date: 14-OCT-2014

Description: Evaluate the outcome data for systemic lupus erythematosus (SLE) subjects who became pregnant while exposed to belimumab during Phase 2–4 clinical trials as well as spontaneous pregnancies reported in patients who were receiving marketed belimumab, and correlate the outcomes with relevant confounders in the SLE population.

Subject: Systemic Lupus Erythematosus, SLE, GSK1550188, meta-analysis, pregnancy, belimumab

Author:

[redacted]
Intern, R&D Medical Affairs
Date:01-OCT-2014

Contributors:

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Manager Statistics
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Approved Via E-mail by:

Email approval on file

[redacted]
Global Medical Affairs Leader, Benlysta
Date:14-OCT-2014

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ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse event
BPR	Belimumab Pregnancy Registry
CDC	Centers for Disease Control and Prevention
CEDD	Corrected estimated date of delivery
CI	Confidence interval
CMG	Case Management Group
EDD	Estimated date of delivery
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HCP	Health care provider
LMP	Last menstrual period
LTF	Lost to follow-up
PGA	Physician Global Assessment
SAE	Serious adverse event
SDI	SLICC/ACR Damage Index
SGA	Small for gestational age
SLE	Systemic Lupus Erythematosus
TLF	Table, listing, figure
WHO	World Health Organization

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1. INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic and progressive autoimmune disease typically requiring lifelong treatment. Pregnancy in women with SLE is associated with significant maternal and foetal morbidity, including spontaneous abortion, pre-eclampsia, intrauterine growth restriction, foetal death, and pre-term delivery [Molad, 2005]. More individuals with SLE 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]. Individuals with SLE testing positive for anti-cardiolipin (aCL) antibodies are at the highest risk of spontaneous abortions and poor foetal outcome [Cortez Hernandez, 2002] with a reported foetal loss rate in the literature of between 15-25% [Rahman, 1998; Andrade, 2008; Yasmeen, 2001; Clowse, 2005]. 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].

Belimumab is a human immunoglobulin-Gγ monoclonal antibody that inhibits the biologic activity of soluble B-lymphocyte stimulator [BLyS]. In the BLISS clinical trials, subjects with autoantibody-positive SLE were randomized to treatment with placebo or belimumab 1mg/kg or 10mg/kg, while also receiving standard SLE therapy. The SLE Responder Index (SRI) response rate at Week 52 was significantly improved in patients treated with belimumab compared with placebo [Navarra, 2009].

There are no adequate, well-controlled studies of the use of belimumab in pregnant women or published data reporting pregnancy outcomes for women with SLE who were exposed to belimumab in the preconception period or during pregnancy. It is known that belimumab crosses the placenta in pregnant monkeys in concentrations that result in reversible pharmacologic activity in fetuses and newborn monkeys. Overall human IgG is known to cross the placental barrier and belimumab may cause a reduction in the number of fetal B cells. Secreted concentrations into breast milk were low in two female adult monkeys [Auyeung-Kim, 2009].

Belimumab has an FDA class C pregnancy category. Human pregnancy data is available from GSK SLE phase II to III clinical trials on belimumab [Powell, 2014]. In these trials, women of childbearing potential with SLE were required to either be abstinent or use birth control and in the event of pregnancy, subjects were withdrawn from the study. Nonetheless, there were 95 pregnancies in these studies as of 14 March 2014. Of the 83 pregnancies whose outcome was known, 24% underwent elective termination of pregnancy (none due to anomaly), 28% had spontaneous miscarriage, 2.4% had stillbirth, and 42% had live birth without congenital anomaly. Three (3.6%) of the live births resulted in a congenital anomaly. The long-term effects, if any, on infants exposed to belimumab in utero are unknown. Healthcare providers and patients need belimumab preganancy-related data to make informed decisions regarding reproductive health. In the published pregnancy outcomes to date, belimumab treatment was discontinued when the pregnancy was recognized. However, in some ongoing clinical trials, it is no longer mandatory to discontinue belimumab treatment in pregnancy. The decision is left to the discretion of the treating physician.

Purpose

The purpose of this meta-analysis is to evaluate maternal, foetal, and infant outcome data for subjects with systemic lupus erythematosus (SLE) who were exposed to belimumab during pregnancy.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective is to determine if there is an increase in birth defects in infants born to women with SLE who were exposed to belimumab during pregnancy. A full listing of trials appears in Section 11.1.

Secondary outcomes including adverse maternal and infant outcomes, e.g. spontaneous miscarriage, preterm birth and stillbirth, will also be evaluated.

2.2. Endpoints

2.2.1. Primary Endpoint

The primary endpoint is the overall frequency (n, %) of birth defects per live births for unblinded reports in women with SLE who received belimumb during pregnancy.

2.2.2. Secondary Endpoints

Secondary endpoints include:

- Types of birth defects among live births: Chromosomal, cardiovascular, musculoskeletal to include limb defects, urogenital, neural tube defects, gastrointestinal, and other structural defects (including cleft lip and cleft palate)
- Pregnancy outcomes(per all pregnancies)
- Rates of spontaneous miscarriage
- Rates of births including live term and pre-term births as well as rates of stillbirths
- Rates of elective pregnancy termination

3. DATA SOURCES/STUDIES INCLUDED

Data will come from the following sources:

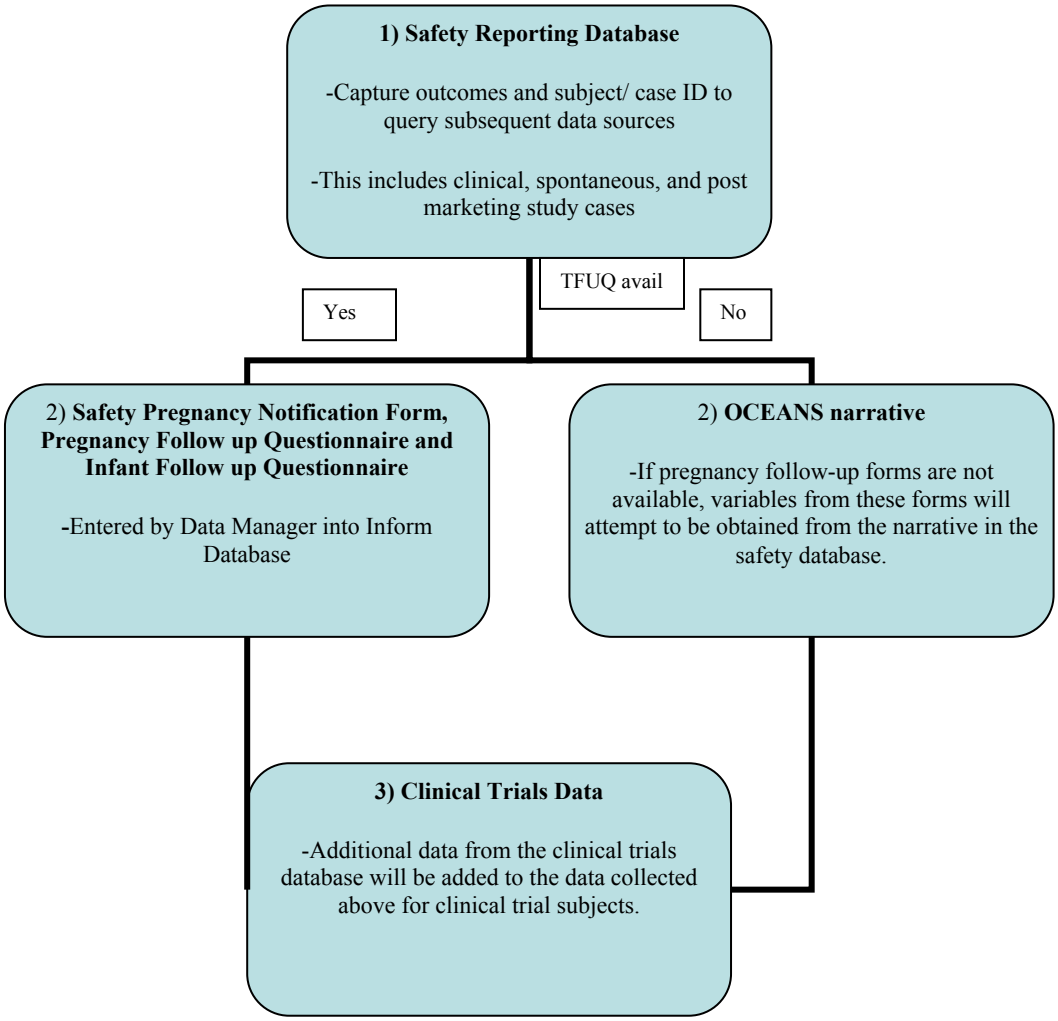
- GSK safety reporting database (OCEANS/ Argus) including data fields and narrative comments.
- Pregnancy Notification Form, Pregnancy Follow up Questionnaire and Infant Follow up Questionnaire.

- Clinical Trial Data in which pregnancy occurred.

A full list of the clinical trials is given in Section 11.1. This list may be updated as additional pregnancies occur. Variables to be extracted from each specified data source are listed in Section 11.2.

Individual pregnancies will be identified from the safety reporting database, and appropriate data will be collected as outlined in Figure 1. Clinical trial data are collected from all of these specified data sources while spontaneous and post marketing data will come only from the safety database and follow up questionnaires.

Figure 1 Summary of Data Sources



4. PLANNED ANALYSES

All data will be summarized using descriptive statistics. Continuous variables will be summarized by number of participants, mean, standard deviation (SD), median, lower quartile, upper quartile, minimum and maximum unless otherwise stated. Categorical

variables will be summarized by number and percentage in each category. Missing data will be displayed as a separate category where appropriate. The denominator for all percentages will reflect the number of participants within the cohort, unless otherwise stated (e.g. excluding lost to follow-up (LTF)). Section 11.3 lists all planned summaries for the study. All data analyses and reporting will be performed using SAS Version 9.3 [SAS Institute Inc, 2011].

Missing Dates

Partial or missing dates for exposures or medical conditions of interest will be presented in listing format unaltered with the missing information displayed as reported. The frequency of birth defects based on timing of belimumab exposure is of interest. As a conservative estimate of birth defects, a missing date will be imputed to correspond to the first trimester of exposure.

Estimating last menstrual period (LMP) or conception date is integral in understanding pregnancy exposure and calculating the duration of drug exposure into pregnancy. LMP will be calculated with priority given to Estimated Date of Delivery (EDD – 280). If EDD is unavailable from the safety database field, safety database narrative, or Pregnancy Notification Form, then LMP will be extrapolated from the most relevant data available in the narrative by an appropriate healthcare professional. If an inconsistent value is given from the three compared sources, an executive decision will be made by the Medical Monitor, SERM physician, or appropriate healthcare professional by applying medical judgment to the available data. If date of conception or LMP is given in month/year format, day will be imputed as the midpoint of the specific month. For example, an estimated LMP of June 2010 will be imputed as June 15 2010.

If maternal date of birth (DOB) is given as birth year, birth date will be imputed as January 1 YEAR. In the interest of understanding advanced maternal age, this is a conservative estimate to estimate advance maternal age.

5. ANALYSIS POPULATION

The primary population will include all subjects from belimumab clinical trials who had an adverse event (AE) of pregnancy while receiving study drug plus standard SLE care. A full listing of clinical trials is given in Section 11.1

The secondary population will include the primary population as well as all post-marketing spontaneous reports of pregnancy while the subject was receiving commercial belimumab.

6. TREATMENT COMPARISONS

For unblinded clinical studies, spontaneous events and open-label or observational post marketing studies the primary treatment comparison will be across belimumab exposure groups based on the last dose received prior to or during pregnancy. Timing of exposure will be calculated by adding 100 days (five elimination half-lives of belimumab) to the last belimumab dose. Comparison groups will be defined by cumulative exposure (e.g., if she was $29^{6/7}$ weeks at the last belimumab dose + 100 days, the pregnancy will be in the category of ≥27 weeks) as prior to pregnancy, 0 - $12^{6/7}$ weeks gestation, $13^{0/7}$ - $26^{6/7}$ weeks gestation, $\geq 27^{0/7}$ weeks gestation. If a patient is started on belimumab during pregnancy such that a cumulative exposure is not applicable, a subgroup will be incorporated as needed. Analyses will be pooled and conducted across dosage and method of drug exposure (intravenous (IV), subcutaneous (SC)).

7. DATA HANDLING CONVENTIONS

7.1. Premature Withdrawal and Missing Data

Subjects who do not have documented pregnancy outcomes and are considered lost to follow up (LTF) will not be included in analyses, but will be documented in descriptive reporting.

7.2. Derived and Transformed Data

Gestational Age will be calculated based on LMP specification and date of delivery or outcome. (Date of delivery – LMP)/7 will be used as calculation and will be reconciled with gestation age reported in the OCEANS Narrative or Pregnancy Notification Form.

Exposure Trimester will be calculated using LMP and defined calendar cut points based on standard definition of trimester. As previously noted, timing of exposure will be assessed as 100 days after last exposure. Comparison groups will be defined by cumulative exposure as prior to pregnancy, 0- - $12^{6/7}$ weeks gestation, $13^{0/7}$ - $26^{6/7}$ weeks gestation, $\geq 27^{0/7}$ weeks gestation. From this categorization, trimester of exposure will be defined as 0 (prior to pregnancy), 1st trimester ($0^{1/7}$ – $12^{6/7}$ weeks gestation), 2nd trimester ($13^{0/7}$ - $26^{6/7}$ weeks gestation), or 3rd trimester ($\geq 27^{0/7}$ weeks gestation).

8. ANALYSES

Analyses will be conducted on unblinded clinical studies, spontaneous events, and open-label or observational post marketing studies.

8.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively. Demographic variables of interest include: participant age, geographic region of study, and baseline disease severity. Age will also be summarized categorically as <35 years or

≥35 years of age based on age at estimated LMP. For available obstetrical history information, outcomes will be summarized with frequencies of previous pregnancy-related conditions. Counts and percentages of the subgroup responses will be displayed in the demographics and baseline characteristic tables for gravidity, parity, number of term and preterm live births, still births, elective terminations, and spontaneous miscarriages.

8.2. Belimumab Dose

For all clinical trial cases, the level of exposure will be categorized as 1mg/kg IV, 4mg/kg IV, 10mg/kg IV or SC by the dose most proximal to the pregnancy onset.

8.3. SLE History at Baseline

SLE diagnosis details will be displayed in a summary table for all baseline assessments, e.g. age at diagnosis, number of ACR criteria met, Physician Global Assessment (PGA) score, SLICC/ACR Damage Index (SDI) score, and laboratory parameters.

8.4. Medical History

Medical history will be summarized. For each condition, the count and percentage will be provided overall, at baseline (prior to conception), at the time the pregnancy is initially reported, and ongoing during pregnancy.

8.5. SLE Related Outcomes

Laboratory parameters, including autoantibody status, complement levels, platelet count, serum creatinine, and urine protein values (when reported) may include the most recent laboratory results prior to conception, at the time the pregnancy is initially reported, at end of 2nd trimester follow-up, and at the time of pregnancy outcome. For the continuous parameters, descriptive statistics will be displayed at each time point as well as for the change values at each time point compared to the most recent result prior to conception.

The PGA and/or SELENA SLEDAI scores when available will be summarized as other continuous variables reporting the mean, standard deviation, median, minimum and maximum value, and the first and third quartile values.

All previously defined demographic and baseline characteristics will include the LTF subgroup and unblinded subjects and be stratified by study type (clinical, spontaneous, post marketing).

8.6. Subgroup Analyses

Table 1 below defines the subgroups of interest that will be used for additional summaries of the primary and secondary outcomes.

Table 1 Subgroups

Subgroup	Definition	Outcomes
Lost to Follow-up (Pregnancy)	Participants with no pregnancy outcome or birth data	Medical History, Maternal Age at LMP, SLE History, Geographic Region
Clinical[1] and Spontaneous cases	Participants grouped by clinical pregnancy and spontaneous event (including spontaneous report and post marketing surveillance).	Primary and Secondary Endpoints
Level of Belimumab Exposure	Defined using exposure dosage proximal to pregnancy start.	Primary and Secondary Endpoints in clinical subjects only
Maternal Age	<35 years and >=35 years based on age at estimated LMP	Primary and Secondary Endpoints
Geographical Region	North America, Europe, Rest of World (Asia, South America, Mexico)	Primary and Secondary Endpoints
Disease Severity 1	PGA >= 2 before pregnancy	Primary and Secondary Endpoints
Disease Severity 2	SDI > 1 before pregnancy	Primary and Secondary Endpoints
Immunosuppressants / Concomitant Medications	Concomitant medications and potential groupings of steroids, antimalarials and immunosuppressants (i.e., Steroids only, antimalarial only, steroids + antimalarials, Steroids + antimalarials +immunosuppressants, and all of their combinations). These will be reviewed by the medical monitor or healthcare professional for accuracy	Primary and Secondary Endpoints
Pregnancy Drug Category D or X	Any concomitant medication which is in categories D or X for pregnancy safety. Reviewed by medical monitor for accuracy	Primary and Secondary Endpoints

[1]Clinical and Spontaneous report will be compared to the BPR analysis, but BPR subjects will be excluded from these analyses.

All outcome data will be stratified by the trimester of exposure to belimumab at 5 half-lives (100 days) after last dose. Categories for timing of belimumab exposure are as follows:

- Prior to conception
- 1st trimester
- 2nd trimester
- 3rd trimester

All data summaries will include treatment comparisons of the cumulative timing of belimumab exposure.

8.7. Exposures and Outcomes

8.7.1. Belimumab

Each exposure to belimumab during the time period of interest is captured for all subjects. The time period of interest includes the four months prior to conception through the entire pregnancy duration. These data, including dose, route, and date of treatment will be reported in a listing.

Subjects with exposure in more than one time point will be counted for each of the appropriate time points. Additionally data will be stratified by dose prior to delivery and delivery method (IV, SC).

8.7.2. Primary Endpoint: Birth Defects

Each birth defect will be classified as known chromosomal or syndromic, or specific organ system defect (e.g. cardiovascular, musculoskeletal to include limb defects, urogenital, neural tube defects, gastrointestinal, and other structural defects (including cleft lip and cleft palate)). The prevalence of birth defects will be calculated as the percentage of total birth defects and by organ system from the total number of live births in the study population and then also stratified by subgroup. Fetal losses with reported birth defects occurring at or after 20 weeks gestation will be included in the numerator of the estimate of risk for birth defects to increase sensitivity.

Birth defect and pregnancy outcome prevalence rates will be calculated. Confidence intervals for birth defect prevalence will be calculated under the exact binomial distribution assumption. A summary table will include birth defect prevalence rates and 95% confidence intervals. Results will also be stratified by timing of exposure and subgroup as previously defined.

8.7.3. Secondary Endpoints: Pregnancy Outcomes

Each pregnancy outcome is defined as one of the following: live birth, neonatal death, stillbirth, spontaneous miscarriage, elective termination, ectopic pregnancy, and molar pregnancy. Prevalence rates and 95% confidence intervals will be summarized for the primary and secondary pregnancy outcomes.

Because the prevalence of preterm birth is elevated in multiple gestations, these cases will be excluded or stratified in the analysis of preterm birth outcomes. In all other pregnancy outcome analysis, multiples will be included independently in analysis.

All pregnancy outcomes will be summarized by the following subgroups:

- Maternal Age
- Region
- PGA Score (≥2)
- SDI (>1)(
- Concomitant Medications and Pregnancy Drug Category D or X

Result will also be presented by timing of belimumab exposure for the overall summaries and within each subgroup.

9. INTERIM ANALYSES

Interim analysis will be conducted annually to coincide with the Belimumab Pregnancy Registry (BPR) scientific advisory committee meetings. Each interim analysis will be based on cumulative data of the registry database as of a prospectively-defined cut-off date.

The first database lock will coincide with the Annual Safety Report on clinical trials of belimumab with AE events of pregnancy on or before March 8 2014. This report will include all of the discussed analysis but will only include clinical cases which are not LTF. Subsequent analysis will include LTF and spontaneous pregnancy events.

10. REFERENCES

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11. ATTACHMENT

11.1. List of Trials

Studies included are: BEL110751, BEL110752, BEL112232, BEL112233, BEL112234, BEL112341, BEL113750, BEL114054, BEL114055, BEL114243, BEL114333, BEL114424, BEL114448, BEL115123, BEL115466, BEL115467, BEL115470, BEL115471, BEL116119, BEL116472, HGS1006-C1058, LBRA01, LBRA99, LBSL01_M, LBSL01_S, LBSL02, and LBSL99.

Subjects in the study BEL112341, BEL113750, BEL114054, BEL115123, BEL115466, BEL115467 and BEL115471 are currently blinded. For BEL112341, BEL113750 and BEL115471, 66.6% of subjects are randomly assigned to the belimumab group and 33.3% of subjects are randomly assigned to the Placebo group. For BEL114054, BEL114424, BEL115123, BEL115466 and BEL115467, subjects are randomly assigned in 1:1 ratio.

11.2. Variables to be Extracted

OCEANS Database VARIABLE CODE	DESCRIPTION
OCEANS ID	ARGUS
Case Type	Case Type(clinical/spontaneous/post marketing)
Country	Country
Protocol_ID	Protocol ID
Subject_ID	Subject ID
Subject site and ID	Subject site and ID
Inv #	Investigator ID
Event PT	Event PT
Outcome (Event Level)	Outcome (Event Level)
Relationship To Drug (Event Level)	Relationship To Drug (Event Level)
Severity	Severity
Seriousness Assessment (Event Level)	Seriousness Assessment (Event Level)
Reason for Seriousness (Case Level)	Reason for Seriousness (Case Level) (Example hospitalization)
Pregnancy Outcome (Case Level)	Pregnancy Outcome (Case Level)
Drug Dose	Beli Drug Dose (1,4,10 mg/kg)
Drug Action	Drug Action (Was drug discontinued?)
Date Stopped	Date Stopped
D_DOB	Mother Date of Birth from OCEANS
D_LMP	Last menstrual period
First Dose Date	First Study Drug Dose Date
Last Dose Date	Last Study Drug Dose Date
Medical History	Medical History
Birth Weight in lbs	Birth Weight in pounds
Gestation Age	Gestation age at delivery
Estimated Date of Delivery	Estimated delivery date DDMMYY

TPNF VARIABLE CODE	DESCRIPTION
Protocol ID	
Subject ID	
Country Of Reporter	
SG_M_YOB	Maternal year of birth YYYY
SG_LMP	Last menstrual period
SG_EST_DELIVERY	Estimated delivery date DDMMYY
SG_ULT_DELIVERY	Corrected estimates date of delivery by ultrasound DDMMYY
SG_CONTRACEPTION	Was mother using contraception
SG_CONTRACEPTION_TEXT	TEXT What type of contraception if YES to SG_CONTRACEPTION
SG_PREV_PREG_PRTRM	Number of previous preterm pregnancies
SG_PREV_PREG_TRM	Number of previous term pregnancies
SG_PREV_BIRTH	Number of previous normal births
SG_PREV_STLLBRTH	Number of previous still births
SG_PREV_BD	Number of previous pregnancies with birth defects
SG_PREV_MISCRRG	Number of previous spontaneous miscarriage
SG_PREV_ECTPIC	Number of previous ectopic pregnancies
SG_PREV_MLR	Number of previous molar pregnancies
SG_PREV_ELCTVE_TERM	Number of previous elective terminations
SG_PREV_NEONATAL_DTH	Number of previous neonatal deaths
SG_PREV_TEXT	TEXT Number of previous other previous pregnancy outcomes
SG_SCREENING_N	NUMBER of screening performed- This field would auto populate the correct number of repetitions of the next 3 fields.
SG_SCREENING	Screening test name
SG_SCREENING_TESTDATE	Screening test date DDMMYY
SG_SCREENING_TEXT	Screening test description of abnormality if present (could this be used to make a positive/negative screen field?)
SG_HYPRTNSN	Maternal hypertension present prior to conception?
SG_TYPE1_DIAB	Maternal Type 1 Diabetes Mellitus present prior to conception?
SG_TYPE2_DIAB	Maternal Type 2 Diabetes Mellitus present prior to conception?
SG_PUL_HYPER	Maternal pulmonary hypertension present prior to conception?
SG_RLUNG	Maternal restrictive lung disease present prior to conception?
SG_RENAL	Maternal renal failure present prior to conception?
SG_HYPOTHYRD	Maternal hypothyroidism present prior to conception?
SG_HYPERTHYRD	Maternal hyperthyroidism present prior to conception?
SG_THROMBOSIS	Maternal thrombotic event(s) present prior to conception?

TPNF VARIABLE CODE	DESCRIPTION
SG_THROMBOCYTOPENIA	Maternal thrombocytopenia present prior to conception?
SG_LUPUS_FLARE	Maternal lupus flare requiring pulse steroids present prior to conception?
SG_PROTEINURIA	Maternal proteinuria present during prior to pregnancy?
SG_GES_DIAB	Maternal gestational diabetes present during prior to pregnancy
SG_ECLAMP	Maternal eclampsia present during prior to pregnancy
SG_DRUG_N	NUMBER of drugs taken- This field would auto populate the correct number of repetitions of the next 3 fields.
SG_DRUG_NAME	Drug/Substance name
SG_DRUG_ROUTE	Drug route
SG_DRUG_DOSE	Drug daily dose
SG_DRUG_START	Drug start date DDMMYY
SG_DRUG_STOP	Drug stop date DDMMYY
SG_DRUG_TEXT	Drug text field(reason for medication)
SG_WITHDRAWN	Was the subject withdrawn from study as a result of this pregnancy?
SG_ANA_BASE_DATE	ANA Autoantibody test baseline date DDMMYY
SG_ANA_BASE_RESULT	ANA Autoantibody test baseline result
SG_ANA_PRECON_DATE	ANA Autoantibody test last preconception date DDMMYY
SG_ANA_PRECON_RESULT	ANA Autoantibody test last preconception result
SG_DSDNA_BASE_DATE	anti-dsDNA Autoantibody test baseline date DDMMYY
SG_DSDNA_RESULT	anti-dsDNA Autoantibody test baseline result
SG_DSDNA_PRECON_DATE	anti-dsDNA Autoantibody test last preconception date DDMMYY
SG_DSDNA_PRECON_RESULT	anti-dsDNA Autoantibody test last preconception result
SG_RO_BASE_DATE	anti-Ro Autoantibody test baseline date DDMMYY
SG_RO_BASE_RESULT	anti-Ro Autoantibody test baseline result
SG_RO_PRECON_DATE	anti-Ro Autoantibody test last preconception date DDMMYY
SG_RO_PRECON_RESULT	anti-Ro Autoantibody test last preconception result
SG_LA_BASE_DATE	anti-La Autoantibody test baseline date DDMMYY
SG_LA_BASE_RESULT	anti-La Autoantibody base test result
SG_LA_PRECON_DATE	anti-La Autoantibody test last preconception date DDMMYY
SG_LA_PRECON_RESULT	anti-La Autoantibody test last preconception date test result
SG_IGG_BASE_DATE	aCl(IgG) Autoantibody test baseline date DDMMYY

TPNF VARIABLE CODE	DESCRIPTION
SG_IGG_BASE_RESULT	aCl(IgG) Autoantibody test baseline result
SG_IGG_PRECON_DATE	aCl(IgG) Autoantibody test last preconception date DDMMYY
SG_IGG_PRECON_RESULT	aCl(IgG) Autoantibody test last preconception result
SG_IGA_BASE_DATE	aCL (IgA) Autoantibody test baseline date DDMMYY
SG_IGA_BASE_RESULT	aCL (IgA) Autoantibody test baseline result
SG_IGA_PRECON_DATE	aCL (IgA) Autoantibody test last preconception date DDMMYY
SG_IGA_PRECON_RESULT	aCL (IgA) Autoantibody test last preconception result
SG_IGM_BASE_DATE	aCl (IgM) Autoantibody test baseline date DDMMYY
SG_IGM_BASE_RESULT	aCl (IgM) Autoantibody test baseline result
SG_IGM_PRECON_DATE	aCl (IgM) Autoantibody test last preconception date DDMMYY
SG_IGM_PRECON_RESULT	aCl (IgM) Autoantibody test last preconception result
SG_ANTICOAG_BASE_DATE	Lupus anticoag Autoantibody test baseline date DDMMYY
SG_ANTICOAG_BASE_RESULT	Lupus anticoag Autoantibody test baseline result
SG_ANTICOAG_PRECON_DATE	Lupus anticoag Autoantibody test last preconception date DDMMYY
SG_ANTICOAG_PRECON_RESULT	Lupus anticoag Autoantibody test last preconception result

TFUQ VARIABLE CODE	DESCRIPTION
Protocol ID	
Subject ID	
Country Of Reporter	
SG_STILLBIRTH	Pregnancy status- early termination - stillbirth
SG_FETALDEATH	Pregnancy status- early termination- fetal death
SG_SPON_MISSCARR	Pregnancy status- early termination-spontaneous miscarriage
SG_ELECTIVE_TERM	Pregnancy status- early termination - elective termination
SG_ELECTIVE_TERM_TEXT	TEXT Pregnancy status- early termination - elective termination details
SG_OUTCOME_TEXT	TEXT Pregnancy status- early termination other
SG_BIRTH_NORM	Fetal/Neonatal status - normal
SG_BIRTH_DEFECT	Fetal/Neonatal status - birth defect
SG_BIRTH_DEF_ORIGIN	Fetal/Neonatal status - if birth defect diagnosed, is the origin of defect known?
SG_BIRTH_DISORDER	Fetal/ Neonatal status - other disorder
SG__DOB	Infant - date of birth/miscarriage/ termination
SG_GA	Infant - Gestational weeks at birth/ miscarriage/ termination
SG_SEX	Infant - sex (1= male, 0=female, 2= ambiguous)
SG_BIRTH_LENGTH	Infant- birth length
SG_BIRTH_LENGTH_UNIT	Infant - birth length units (either cm or inches)
SG_BIRTH_WEIGHT	Infant - weight
SG_BIRTH_WEIGHT_UNIT	Infant - weight units (either grams or ounces?)
SG_HEAD_CIRCUM	Infant - head circumference
SG_HEAD_CIRCUM_UNIT	Infant - head circumference (SHOULD be in cm)
SG_APGAR_1	Infant - APGAR at 1 minute
SG_APGAR_5	Infant - APGAR at 5 minute
SG_APGAR_10	Infant - APGAR at 10 minute
SG_PREG_PUL_HYPER	Pulmonary Hypertension -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_PUL_HYPER_STARTDATE	Pulmonary Hypertension start date DDMMYY
SG_PREG_PUL_HYPER_STOPDATE	Pulmonary Hypertension stop date DDMMYY
SG_PREG_RENALFAIL	Renal Failure -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_RENALFAIL_STARTDATE	Renal Failure start date DDMMYY
SG_PREG_RENALFAIL_STOPDATE	Renal Failure stop date DDMMYY
SG_PREG_HYPOTHYRD	Hypothyroidism -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_HYPOTHYRD_STARTDATE	Hypothyroidism start date DDMMYY
SG_PREG_HYPOTHYRD_STOPDATE	Hypothyroidism stop date DDMMYY
SG_PREG_HYPERTHYRD	Hyperthyroidism -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_HYPERTHYRD_STA	Hyperthyroidism start date DDMMYY

TFUQ VARIABLE CODE	DESCRIPTION
RTDATE	
SG_PREG_HYPERTHYRD_STOPDATE	Hyperthyroidism stop date DDMMYY
SG_PREG_RLUNG	Restrictive Lung Disease -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_RLUNG_STARTDATE	Restrictive Lung Disease start date DDMMYY
SG_PREG_RLUNG_STOPDATE	Restrictive Lung Disease stop date DDMMYY
SG_PREG_THROMBOSIS	Thrombotic Event(s) -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_THROMBOSIS_STARTDATE	Thrombotic Event(s) start date DDMMYY
SG_PREG_THROMBOSIS_STOPDATE	Thrombotic Event(s) stop date DDMMYY
SG_PREG_THROMBOCYTOPENIA	Thrombocytopenia -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_THROMBOCYTOPENIA_STARTDATE	Thrombocytopenia start date DDMMYY
SG_PREG_THROMBOCYTOPENIA_STOPDATE	Thrombocytopenia stop date DDMMYY
SG_PREG_LUPUS_FLARE	Lupus Flare requiring Pulse Steroids -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_LUPUS_FLARE_STARTDATE	Lupus Flare requiring Pulse Steroids start date DDMMYY
SG_PREG_LUPUS_FLARE_STOPDATE	Lupus Flare requiring Pulse Steroids stop date DDMMYY
SG_PREG_HYPERTENSION	Hypertension -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_HYPERTENSION_STARTDATE	Hypertension start date DDMMYY
SG_PREG_HYPERTENSION_STOPDATE	Hypertension stop date DDMMYY
SG_PREG_TYPE1_DIAB	Type 1 Diabetes Mellitus -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_TYPE1_DIAB_STARTDATE	Type 1 Diabetes Mellitus start date DDMMYY
SG_PREG_TYPE1_DIAB_STOPDATE	Type 1 Diabetes Mellitus stop date DDMMYY
SG_PREG_TYPE2_DIAB	Type 2 Diabetes Mellitus -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_TYPE2_DIAB_STARTDATE	Type 2 Diabetes Mellitus start date DDMMYY
SG_PREG_TYPE2_DIAB_STOPDATE	Type 2 Diabetes Mellitus stop date DDMMYY
SG_PREG_PROTEINURIA	Proteinuria -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_PROTEINURIA_STARTDATE	Proteinuria start date DDMMYY

TFUQ VARIABLE CODE	DESCRIPTION
SG_PREG_PROTEINURIA_STOPDATE	Proteinuria stop date DDMMYY
SG_PREG_GES_DIAB	Gestational Diabetes -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_GES_DIAB_STARTDATE	Gestational Diabetes start date DDMMYY
SG_PREG_GES_DIAB_STOPDATE	Gestational Diabetes stop date DDMMYY
SG_PREG_PREECLAMP	Preeclampsia-Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_PREECLAMP_STARTDATE	Preeclampsia start date DDMMYY
SG_PREG_PREECLAMP_STOPDATE	Preeclampsia stop date DDMMYY
SG_PREG_ECLAMP	Eclampsia -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_ECLAMP_STARTDATE	Eclampsia start date DDMMYY
SG_PREG_ECLAMP_STOPDATE	Eclampsia stop date DDMMYY
SG_PREG_ABRUPTN	Placental abruption -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_ABRUPTN_STARTDATE	Placental abruption start date DDMMYY
SG_PREG_ABRUPTN_STOPDATE	Placental abruption stop date DDMMYY
SG_PREG_CHORIOAMNTS	Chorioamnionitis -Medical condition present during pregnancy (New Onset, Recurrence, Worsening)
SG_PREG_CHORIOAMNTS_STARTDATE	Chorioamnionitis start date DDMMYY
SG_PREG_CHORIOAMNTS_STOPDATE	Chorioamnionitis stop date DDMMYY
SG_PREGDRUG_N	NUMBER of drugs taken- This field would auto populate the correct number of repetitions of the next 3 fields.
SG_PREGDRUG_NAME	Drug/Substance name
SG_PREGDRUG_ROUTE	Drug route
SG_PREGDRUG_DOSE	Drug daily dose
SG_PREGDRUG_START	Drug start date DDMMYY
SG_PREGDRUG_PRIOR	Was drug taken prior to study start?
SG_PREGDRUG_STOP	Drug stop date DDMMYY
SG_PREGDRUG_TEXT	Drug text field (reason for medication)

COIMS Narrative VARIABLE CODE	**DESCRIPTION**
LMP KNOWN	Is LMP known via OCEANs report or narrative then Y, else N
LMP_MATCH	OCEANs and CIOMS LMP report do not match then (N)
MARCY_LMP	Last Menstrual Period
MARCY_CONCEPTION	Date of Conception(if noted)
MARCY_AGE	Mother Age from narrative
MARCY_DUE_DATE	Due date calculated from LMP UNLESS otherwise noted in narrative
MARCY_TREAT_ASSIGNMENT	IF in continuation trial dose
MARCY_DATE_CONTINUATION	Start in continuation
MARCY_DOD	Date of delivery or event
MARCY_GA	Gestational age calculated by DOD - LMP / 7 unless otherwise noted in narrative
MARCY_CONCOM_MED_N	Number of concomitant medications from narrative
MARCY_CONCOM_MED	List of RELEVANT concomitant medications from narrative
MARCY_MED_HYDROXYCHLOROQ	Concomitant med hydroxychloroquine
MARCY_MED_METHOTREX	Concomitant med methotrexate
MARCY_MED_AZATHIO	Concomitant med azathioprine
MARCY_MED_MYCOPHENO	Concominant med mycophenolate
MARCY_MED_CYCLOPHOSPHAMIDE	Concominant med cyclophosphamide
MARCY_MED_CYCLOSPORINE	Concominant med cyclosporine
MARCY_MED_STERIOD	Concominant med steroids
MARCY_MED_RITUXIMAB	Concominant med rituximab
MARCY_MED_TACROLIMUS	Concominant med tacrolimus
MARCY_MED_ABATACEPT	Concominant med abatacept(orencia)
MARCY_MED_CONTINUED	Is medication listed as continued through pregnancy
MARCY_M_INFECTION	Maternal infection
MARCY_N_INFECTION	Neonatal infection
MARCY_PREV_PREG_PRTRM	Previous preterm pregnancy
MARCY_PREV_PREG_TRM	Previous term pregnancy
MARCY_PREV_PREG_TOTAL	Previous TOTAL pregnancies
MARCY_PREV_BIRTH	Number of previous normal births
MARCY_PREV_STLLBRTH	Number of previous still births
MARCY_PREV_BD	Number of previous pregnancies with birth defects
MARCY_PREV_MISCRRG	Number of previous spontaneous miscarriage
MARCY_PREV_ECTPIC	Number of previous ectopic pregnancies
MARCY_PREV_MLR	Number of previous molar pregnancies
MARCY_PREV_ELCTVE_TERM	Number of previous elective terminations
MARCY_PREV_NEONATAL_DTH	Number of previous neonatal deaths
MARCY_PREV_TEXT	TEXT Number of previous other previous pregnancy outcomes
MARCY_M_COMPLICATION	Maternal complication
MARCY_N_COMPLICATION	Neonatal complication
MARCY_RELEVANT_TEXT	Relevant text from narrative

Clinical Database VARIABLE CODE	DESCRIPTION
Protocol	Protocol No
County	Country
Site	Site Number
Subject_ID	Subject ID
First Dose Date	Date of first dose in parent study
Parent_treat	Parent study Treatment Assignment if in continuation trial
First Dose Date Continuation	Date of first dose in Continuation Trial (if applicable)
Last Dose Date	Date of last study drug dose
Medical_History	Medical History
Con_Meds	Concomitant Medications at onset of pregnancy
Recent_Anticardiolipin	Most recent Anticardiolipin Antibody
Date_Anticardiolipin	Date of most recent Anticardiolipin Antibody
Positive_Anticardiolipin	Anticardiolipin Antibody ever positive
Baseline_Anticardiolipin	Anticardiolipin Antibody at baseline
Recent_complement	Most recent complement levels prior to pregnancy (low, normal)
Date_complement	Date of most recent complement level prior to pregnancy
Pregnancy_complement	Complement levels during pregnancy (if available)
Baseline_complement	Complement levels at baseline
Baseline_SELENA	SELENA SLEDAI score at baseline
Recent_SELENA	SELENA SLEDAI score most recent prior to pregnancy
Date_SELENA	Date of most recent SELENA SLEDAI assessment prior to pregnancy
Pregnancy_SELENA	SELENA SLEDAI score during pregnancy
Date_SELENA_preg	Date of SELENA SLEDAI score during pregnancy
Maternal_infection	Serious Maternal Infections Reported
Maternal_age	Maternal Age(Birth date)
SLICC_damage_index	Measure of organ dysfunction

11.3. Table of Contents for Data Displays

Number	Title
5.01	Summary of Demographic Characteristics
5.02	Summary of Baseline Disease Characteristics
5.03	Summary of Baseline Medical History
5.04	Summary of Concomitant Medications
5.05	Summary of Infections
5.06	Summary of Disease Characteristics Prior to Pregnancy Reference Date
9.1	Listing of Demographic Characteristics

Number	Title
1.1	Summary of Birth defect overall prevalence and clinical study descriptions
1.2	Summary of Birth defect by Belimumab dose
1.3	Summary of Birth defect by Disease Severity
1.4	Summary of Birth defect by Medication
1.5	Summary of Birth defect by Organ System

Number	Title
2.1	Summary of Chromosomal Birth defect Overall Prevalence and clinical study descriptions
2.2	Summary of Chromosomal Birth defect by Belimumab dose
2.3	Summary of Chromosomal Birth defect by Disease Severity
2.4	Summary of Chromosomal birth defect by Medication

Number	Title
3.1	Summary of Cardiovascular Birth defect Overall Prevalence and clinical study descriptions
3.2	Summary of Cardiovascular Birth defect by Belimumab dose
3.3	Summary of Cardiovascular Birth defect by Disease Severity
3.4	Summary of Cardiovascular birth defect by Medication

Number	Title
4.1	Summary of Musculoskeletal Birth defect Overall Prevalence and clinical study descriptions
4.2	Summary of Musculoskeletal Birth defect by Belimumab dose
4.3	Summary of Musculoskeletal Birth defect by Disease Severity
4.4	Summary of Musculoskeletal birth defect by Medication

Number	Title
5.1	Summary of Urogenital Birth defect Overall Prevalence and clinical study descriptions
5.2	Summary of Urogenital Birth defect by Belimumab dose
5.3	Summary of Urogenital Birth defect by Disease Severity
5.4	Summary of Urogenital birth defect by Medication

Number	Title
6.1	Summary of Neural Tube Birth defect Overall Prevalence and clinical study descriptions
6.2	Summary of Neural Tube Birth defect by Belimumab dose
6.3	Summary of Neural Tube Birth defect by Disease Severity
6.4	Summary of Neural Tube birth defect by Medication

Number	Title
7.1	Summary of Gastrointestinal Birth defect Overall Prevalence and clinical study descriptions
7.2	Summary of Gastrointestinal Birth defect by Belimumab dose
7.3	Summary of Gastrointestinal Birth defect by Disease Severity
7.4	Summary of Gastrointestinal birth defect by Medication

Number	Title
8.1	Summary of Other Structural Birth defect Overall Prevalence and clinical study descriptions
8.2	Summary of Other Structural Birth defect by Belimumab dose
8.3	Summary of Other Structural Birth defect by Disease Severity
8.4	Summary of Other Structural birth defect by Medication

Number	Title
9	Summary of Birth Outcomes

Number	Title
10.1	Summary of Live Birth Overall Prevalence and clinical study descriptions
10.2	Summary of Live Birth by Belimumab dose
10.3	Summary of Live Birth by Disease Severity
10.4	Summary of Live Birth by Medication

Number	Title
11.1	Summary of Preterm Birth Overall Prevalence and clinical study descriptions
11.2	Summary of Preterm Birth by Belimumab dose
11.3	Summary of Preterm Birth by Disease Severity
11.4	Summary of Preterm Birth by Medication

Number	Title
12.1	Summary of Spontaneous Miscarriage Overall Prevalence and clinical study descriptions
12.2	Summary of Spontaneous Miscarriage by Belimumab dose
12.3	Summary of Spontaneous Miscarriage by Disease Severity
12.4	Summary of Spontaneous Miscarriage by Medication

Number	Title
13.1	Summary of Stillbirth Overall Prevalence and clinical study descriptions
13.2	Summary of Stillbirth by Belimumab dose
13.3	Summary of Stillbirth by Disease Severity
13.4	Summary of Stillbirth by Medication

Number	Title
14.1	Summary of Elective Abortion Overall Prevalence and clinical study descriptions
14.2	Summary of Elective Abortion by Belimumab dose
14.3	Summary of Elective Abortion by Disease Severity
14.4	Summary of Elective Abortion by Medication

Number	Title
15	Summary of Previous Pregnancy Conditions by Birth Outcome
16	Summary of Disease Severity Descriptive Statistics

11.4. Data Display Specifications

In general, summaries of clinical data will follow the appropriate IDSL standard. All tables, listings, and figures (TLF) will be produced in landscape format with font size 10.

11.5. Table Shells

Table shells are attached as a separate file

SPONSOR SIGNATORY SIGNATURE PAGE

STUDY TITLE: Meta-Analysis Results Report for Study Number 201182, GSK1550188, SLE, Pregnancy Analysis

Study: 201182 Development Phase: [IV]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted] MD

Title of Sponsor Signatory: GSK, Director, Global Clinical Safety and Pharmacovigilance

Signature: [redacted]

Date: 16 November 2015