**Protocol**

**Study ID:** 213928

**Official Title of Study:** The Belimumab Pregnancy Exposure Study: An OTIS Autoimmune Diseases in Pregnancy Project

**Date of Document:** 29 Mar 2022

# TITLE PAGE

**Division:** Pharma Research and Development

**Information Type:** Epidemiology PASS Protocol

| | |
|---|---|
| **Title:** | The Belimumab Pregnancy Exposure Study: An OTIS Autoimmune Diseases in Pregnancy Project |
| **Compound Number:** | GSK1550188 |
| **Development Phase** | IV |
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| **Subject:** | Safety in pregnancy |
| **Author(s):** | PPD ; PPD ; PPD ; PPD ; |

**Sponsor Signatory Details**

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# PASS information

| | |
|---|---|
| **Title** | The Belimumab Pregnancy Exposure Study: An OTIS Autoimmune Diseases in Pregnancy Project |
| **Protocol version identifier** | 1 |
| **Date of last version of protocol** | N/A |
| **EU PAS (ENCEPP) register number** | To be confirmed |
| **Active substance** | Belimumab |
| **Medicinal product** | BENLYSTA |
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| **Marketing authorisation holder(s)** | GlaxoSmithKline |
| **Joint PASS** | No |
| **Research question and objectives** | To monitor planned and unplanned pregnancies exposed to belimumab and to evaluate the possible teratogenic effect of this medication relative to the primary pregnancy outcomes of major birth defects. Secondary outcomes also evaluated in the study include other pregnancy outcomes as well as infant outcomes up to one year of age. |
| **Countries of study** | United States and Canada |
| **Author** | PPD ; PPD ; PPD ; PPD |

# MARKETING AUTHORISATION HOLDER(S)

| | |
|---|---|
| **Marketing authorisation holder(s)** | GlaxoSmithKline (Ireland) Limited<br>12 Riverwalk<br>Citywest Business Campus<br>Dublin 24<br>D24 YK11<br>Ireland |
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# SPONSOR INFORMATION PAGE

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**Sponsor Serious Adverse Events (SAE) Contact Information:**

Refer to Safety Management Plan for details

**Regulatory Agency Identifying Number(s):** Not applicable

# INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:

PPD

Investigator Signature

Date

## Study Advisory Committee

The Belimumab Pregnancy Exposure Study: An OTIS Autoimmune Diseases in Pregnancy Project has an independent scientific committee that consists of representation from the U.S. Centers for Disease Control and Prevention Center for Birth Defects and Developmental Disabilities, a maternal-fetal medicine specialist, a geneticist, and disease-specific specialty representative. This standing committee meets annually and reviews all interim data, interim and final study reports. The committee comments on the study progress and poses questions that arise, which are addressed by the investigators.

## TABLE OF CONTENTS

**PAGE**

# 1. LIST OF ABBREVIATIONS

| | |
|---|---|
| aCL | Anticardiolipin |
| ACR | American College of Rheumatology |
| AE | Adverse Event |
| ASQ | Ages and Stages Questionnaire |
| BLyS | B lymphocyte stimulator protein |
| BCMA | B Cell Maturation Antigen |
| CA | California |
| CDC | Centers for Disease Control and Prevention |
| CI | Confidence Interval |
| CMV | Cytomegalovirus |
| EU | European union |
| FDA | Food and drug administration |
| GA | Gestational Age |
| GEE | Generalized estimating equations |
| GSK | GlaxoSmithKline |
| HCP | Healthcare Professional |
| HR | Hazard Ratio |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICMJE | International Committee of Medical Journal Editors |
| Ig | Immunoglobulin |
| IHD | Individual human data |
| IPW | Inverse Probability Weighting |
| IRB | Institutional Review Board |
| IV | Intravenous |
| LMP | Last Menstrual Period |
| MACDP | Metropolitan Atlanta Congenital Defects Program |
| MAH | Market Authorisation Holder |
| MBD | Major Birth Defect |

| | |
|---|---|
| MCM | Major Congenital Malformation |
| MTB | Mother To Baby |
| mg | Milligrams |
| NCHS | National Center for Health Statistics |
| No | Number |
| OTIS | Organization of Teratology Information Specialists |
| PAS | Post-authorization studies |
| PCP | Primary Care Physicians |
| PGA | Physician Global Assessment |
| PS | Propensity Score |
| PTB | Preterm Birth |
| PtGA | Patient Global Assessment |
| RR | Relative Risk |
| SAB | Spontaneous Abortion |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SELENA-SLEDAI | Safety of Estrogen in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index |
| SGA | Small for Gestational Age |
| SLE | Systemic Lupus Erythematosus |
| SMD | Standardized Mean Differences |
| SMP | Safety Management Plan |
| SOP | Standard Operating Procedure |
| SRI | SLE Responder Index |
| TACI | Transmembrane Activator–1 and Calcium Modulator and Cyclophilin Ligand Interactor |
| TNF | Tumor Necrosis Factor |
| UK | United Kingdom |
| US | United States |

**Trademark Information**

| **Trademarks of the GlaxoSmithKline group of companies** |
|---|
| BENLYSTA |

| **Trademarks not owned by the GlaxoSmithKline group of companies** |
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| Jantoven |

# 2. RESPONSIBLE PARTIES

**Sponsor**

The Marketing Authorisation Holder (MAH) will serve as the sponsor of this study. It is the responsibility of the MAH to ensure proper monitoring of the study and compliance with all applicable regulatory guidelines and laws.

Primary contact:

PPD

Benlysta Global Regulatory Affairs Lead
Global Regulatory Affairs
GlaxoSmithKline Research & Development Ltd.

**Study Coordination**

The MAH has contracted with the University of California Research Center for the MotherToBaby/Organization of Teratology Information Specialists (OTIS) to provide scientific leadership and to conduct the study. The OTIS Research Centre will conduct the study with review and input from the MAH.

The OTIS Research Centre will receive referrals from the North American OTIS network of teratogen information counseling services. The North American OTIS network is a network of university and health department-based telephone information centers serving pregnant women and health care providers throughout the U.S. and Canada. The OTIS network receives voluntary reports of pregnancy and exposures from women and health care providers.

Principal Investigator:

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# 3. ABSTRACT

**Protocol Title:** The Belimumab Pregnancy Exposure Study: An OTIS Autoimmune Diseases in Pregnancy Project

**Rational and Background**

Systemic Lupus Erythematosus (SLE) is more common in women than men and most common in women of childbearing age. Belimumab (BENLYSTA) is a human monoclonal antibody that inhibits B lymphocyte stimulator protein (BLyS) indicated as an adjunct to standard therapy for the treatment of active, autoantibody-positive, systemic lupus erythematosus (SLE) aged 5 years and older. Belimumab is given as 10 mg/kg/dose intravenous (IV) infused over 1 hour every 2 weeks for the first 3 doses, then every 4 weeks thereafter in patients aged 5 years and older, or 200 mg by subcutaneous injection every week in adults. Package labeling in the US and Canada comments that the paucity of data concerning pregnancies is insufficient to inform on drug-associated risks to the fetus or mother. Nonetheless, belimumab will be knowingly utilized by pregnant women when they and their doctor believe the risk benefit favors its use. We therefore propose a pregnancy exposure cohort study to assess the safety of belimumab in pregnancy. Information regarding the safety of belimumab in human pregnancy is essential from a public health perspective to help inform clinical practice.

**Research question and Objectives**

The overall aim of the study is to determine whether there is a signal for Benlysta teratogenicity when used during pregnancy. The primary objective of the study is to evaluate belimumab exposure in pregnancy with respect to major birth defects when compared to the background rate in an unexposed SLE cohort. Secondary objectives will include a pattern of minor birth defects, spontaneous abortion (including ectopic/molar pregnancy), elective termination, stillbirth, preterm delivery, small for gestational age (SGA) infants, postnatal growth deficiencies, developmental concerns and serious or infections in live born infants up to one year of age.

**Study Design**

This is a prospective, observational, exposure cohort study of pregnancy outcomes in women exposed to belimumab during pregnancy compared to pregnancy outcomes in women with a diagnosis of SLE who have not used belimumab during pregnancy (but may have been exposed to other medications for the treatment of SLE) (disease comparison group). Pregnant women exposed to belimumab who do not meet the inclusion criteria of this study may be followed as part of an exposure case series. All participants will be recruited via voluntary participant registration following informed consent. Participants may withdraw from the study at any time.

**Population**

The study population includes pregnant women who reside in the US or Canada. Two cohorts of women will be enrolled prospectively: **1)** a belimumab-exposed cohort with exposure to at least one dose of belimumab from 3 months before the first day of the last menstrual period (LMP) to the end of pregnancy; **2)** a disease cohort with SLE who have not been exposed to belimumab from 3 months before the first day of the LMP or throughout pregnancy. Pregnant women exposed to belimumab who do not meet the inclusion criteria of this study may be followed separately as part of an exposure case series

**Variables**

Exposure will be defined as belimumab treatment at any time during pregnancy (from 3 months before the first day of the LMP throughout pregnancy) by maternal report and verified by medical record review, with detailed information on the gestational timing, route of administration, dose, and dates of exposure. The primary outcome variable is major birth defects. Secondary outcome variables include a pattern of minor birth defects, spontaneous abortion (including ectopic/molar pregnancy), elective termination, stillbirth, preterm delivery, SGA and infant outcomes of postnatal growth deficiencies, developmental concerns, and serious or infections in live born infants up to one year of age. These will be obtained by maternal report and verified by medical record review. Potential confounders or covariates to be collected include age, race/ethnicity, body mass

index, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, maternal exposures (including medication, vaccine,vitamin/mineral, and illnesses), prenatal tests, infant complications and pediatric exposures, and measures of SLE disease severity (including SLE specific lab values if available).

**Data Sources**

Information will be obtained through standard maternal interviews conducted in each trimester and postpartum subsequent to study enrollment, and from medical records obtained from obstetric, hospital, pediatric and specialty providers. Data will be recorded on hard copies of forms or electronically, and these records will be retained by Organization of Teratology Information Services (OTIS). These forms are considered the primary data sources for the study. Data from these forms will be extracted and entered into a customized OTIS study database located in the OTIS Research Center and developed specifically for OTIS studies.

**Study Size and Timing**

The target sample size for the cohort study is 200 women in the belimumab-exposed cohort and 200 women in the unexposed disease comparison cohort. Recruitment is planned for 5 years.

**Data Analysis**

Demographic and patient characteristics will be compared between the cohorts. The primary analysis will be a comparison of the birth prevalence rate of major birth defects in live born infants (multiple births are handled as one pregnancy outcome) between the belimumab-exposed cohort and the disease comparison cohort. Secondary outcomes to be evaluated include a pattern of minor birth defects, spontaneous abortion (including ectopic/molar pregnancy), elective termination, stillbirth, preterm delivery, SGA at birth, and infant outcomes (postnatal growth deficiencies, developmental concerns, and serious infections up to one year of age).

A stepwise approach will be used for the analysis: The initial analysis will be descriptive and unadjusted. Where numbers permit, multivariable analyses will be conducted for the primary and secondary analyses to adjust for possible confounders.

The primary assessments of interest are the point estimates and 95% confidence intervals (CI) of major birth defects within the belimumab-exposed group; the estimates will also be calculated for the unexposed disease comparison group. The relative risk and 95% CI (belimumab-exposed vs unexposed) will be estimated to aid in assessment of a signal of teratogenicity.

# 4. AMENDMENTS AND UPDATES

| **GlaxoSmithKline Document Number** | **Date** | **Version** |
|---|---|---|
| TMF-14555546 | **29** Mar 2022 | Original |

# 5. MILESTONES

| **Milestone** | **Planned date** |
|---|---|
| Start of data collection | 2022 |
| End of data collection | 2030 |
| Interim Report 1 | 2023 |
| Interim Report 2 | 2024 |
| Interim Report 3 | 2025 |
| Interim Report 4 | 2026 |
| Interim Report 5 | 2027 |
| Registration in the European Union post-authorisation studies (EU PAS) register | 2022 |
| Final report of study results | 2030 |

# 6. RATIONAL AND BACKGROUND

## 6.1. Background

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

In the US, the estimated average of the reported prevalences of SLE is approximately 10 cases per 10,000 persons, representing about 300,000 patients, and the incidence

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

More patients with lupus are women than men; the female-to-male ratio in the childbearing years has been reported to be as high as 12:1 [Danchenko, 2006]. In women, SLE typically develops between ages 15 and 44 years, and onset is most likely insidious [Danchenko, 2006]. Complications during pregnancy can include lupus flares, worsening or new onset of renal failure, hypertension, preeclampsia, pulmonary embolism, deep vein thrombosis, major infections, bleeding and thrombotic events. Of the 63 women in the Lupus in Minorities; Nature vs. Nurture (LUMINA) cohort who became pregnant during follow-up, 76% developed complications [Andrade, 2006]. Pregnancy remains contraindicated in SLE patients with severe pulmonary hypertension or restrictive lung disease, heart failure, chronic renal failure, previous severe preeclampsia, HELLP (hemolysis, elevated liver enzyme levels and a low platelet count) despite therapy with aspirin and heparin, and in SLE patients with stroke or severe lupus flare within the previous 6 months [Ruiz-Irastorza, 2011]. Complications of lupus pregnancy can be minimized with careful screening and close cooperation across the health care team. Careful attention to the impact of concomitant medications has had a positive impact on the outcome of pregnancies [Ruiz-Irastorza, 2009; Ruiz-Irastorza, 2011].

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

studies [Clowse, 2005; Andrade, 2008], with stillbirths accounting for 2%-4% of these outcomes.

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

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

B-lymphocyte stimulator (BLyS), a 285-amino acid protein and member of the tumor necrosis factor (TNF) ligand superfamily, is a B cell survival factor that inhibits apoptosis and stimulates the differentiation of B cells into immunoglobulin-producing plasma cells [Moore, 1999; Do, 2000]. In humans, soluble BLyS is biologically active and produced primarily by monocytes and activated neutrophils [Moore, 1999; Scapin, 2008]. BLyS can bind to 3 receptors on B lymphocytes: BLyS receptor 3 (BR3; also known as BAFFR), a transmembrane activator–1 and calcium modulator and cyclophilin ligand interactor (TACI), and B cell maturation antigen (BCMA) [Cancro, 2004; Gross, 2000;

Xia, 2000; Yan, 2000]. BLyS is over expressed in patients with SLE and other autoimmune diseases, and BLyS levels correlate with disease activity [Cheema, 2001; Zhang, 2001; Groom, 2002; Mariette, 2003; Petri, 2008; Daridon, 2009]. Belimumab is a recombinant, human, IgG1λ monoclonal antibody that binds soluble BLyS with high affinity and inhibits its biological activity [Baker, 2003]. Following *in vitro* and animal model studies [Belimumab Investigator's Brochure [IB], 2020; 2011N128591_06], belimumab was identified as a potential therapeutic agent for autoimmune diseases in which BLyS may play a role in disease pathogenesis.

Limited data are available from human subjects who received substantial exposure to belimumab during pregnancy, as women who became pregnant in belimumab clinical trials were withdrawn from treatment as soon as the pregnancy was detected through monthly pregnancy screening. However, in a study of prenatal and postnatal development conducted in cynomolgus monkeys, pregnant monkeys received belimumab by IV injection at approximately gestation day 20-22 and every 2 weeks thereafter until parturition [Belimumab Investigator's Brochure [IB], 2020; 2011N128591_06]. Treatment with belimumab was not associated with direct or indirect harmful effects with respect to maternal toxicity, developmental toxicity, or teratogenicity. Treatment-related findings were limited to expected reduction of B cells and IgM in both dams and infants. B-cell numbers recovered after the cessation of belimumab treatment by about 1-year post-partum in adult monkeys and by 3 months of life in infant monkeys. IgM levels in infants exposed to belimumab in utero recovered by 6 months of age. Study data revealed the passage of belimumab across the placenta and excretion of belimumab into the milk of nursing female monkeys. Human Genome Sciences Inc. (HGS) and GlaxoSmithKline (GSK) have completed two Phase 3 studies for the use of belimumab in SLE. In the Phase 3 studies [Navarra, 2011; Furie, 2011] autoantibody-positive patients with active SLE were administered either intravenous (IV) belimumab (1 mg/kg or 10 mg/kg) or placebo in addition to their baseline medications for lupus. Active disease was considered to be a Safety of Estrogen in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) ≥ 6. In the Phase 3 studies, belimumab 10 mg/kg plus standard therapy demonstrated superiority over placebo plus standard therapy in reduction in disease activity as measured by the SLE

responder index (SRI) with an acceptable safety profile. Evidence of benefit in other clinical measures such as reductions in disease activity as measured by SELENA-SLEDAI, severe flare, and reduced steroid use were also observed.

### 6.2. Rationale

Information regarding the safety of belimumab in human pregnancy is essential from a public health perspective as inadvertent pregnancy exposure to belimumab may take place, and safety information for women who may need this medication is necessary to inform clinical practice.

## 7. RESEARCH QUESTION AND OBJECTIVE(S)

The purpose of the Belimumab Pregnancy Exposure Study is to monitor planned and unplanned pregnancies exposed to belimumab and to evaluate the possible teratogenic effect of this medication relative to the primary outcome of major birth defects, the secondary outcome spontaneous abortion (including ectopic and molar pregnancies), stillbirth, elective termination, preterm delivery, and infant outcomes (small for gestational (SGA) age at birth, postnatal growth deficiencies, developmental concerns and serious infections in live born infants to one year of age) and minor birth defect patterns. The overall aim of the study is to determine whether there is a signal for belimumab teratogenicity when compared to the background rate in an unexposed SLE cohort.

## 8. RESEARCH METHODS

### 8.1. Study Design

This is a prospective, observational, exposure cohort study of pregnancy outcomes in women exposed to belimumab during pregnancy (from 3 months prior to the first day of the LMP throughout pregnancy) compared to pregnancy outcomes in women with a diagnosis of SLE who have not used belimumab and may or may not have used other medications for the treatment of their disease during pregnancy (disease comparison group). The study will be conducted by the MotherToBaby/Organization of Teratology Information Specialists (OTIS) Research Center located at the University of California San Diego. The registry relies on voluntary reporting of pregnancy and exposures by

women and health care providers who contact the North American OTIS/MotherToBaby network of teratogen information counselling services.

The study design is appropriate for the study objectives in that mothers are enrolled in the cohort groups before the outcome of pregnancy is known, direct measures of relative and absolute risk can be computed, and a range of adverse pregnancy outcomes can be evaluated.

The study design includes the identification of women with belimumab exposure in pregnancy or in the 3 months before LMP, and one disease comparison group with the same underlying maternal disease but no treatment with belimumab in pregnancy or in the 3 months before LMP. The disease comparison group is essential, in that maternal SLE itself has been associated with a wide variety of adverse pregnancy outcomes (Chakravarty, 2006; Clowse, 2008). If the distribution of underlying disease severity is as similar as possible within the current clinical environment in both the belimumab-exposed and the unexposed disease group, this will allow for best control for confounding by the disease (and disease-severity) with respect to the study outcomes.

Women who agree to enroll will be consented verbally over the telephone and will then complete the initial telephone interview. Depending on the gestational timing of enrollment, a number of subsequent telephone interviews will be conducted during pregnancy and after birth. Medical records for both the women and infant will be obtained and abstracted for information to validate exposures and outcomes and potentially used to assess specific disease related factors that could be confounding factors. Enrolled women will be followed until the completion of pregnancy and live born infants followed up to one year after birth to determine the outcome of pregnancy with respect to primary and secondary study outcomes.

## 8.2. Study Population and Setting

The study population consists of two cohorts of pregnant women: **cohort 1**-Belimumab exposed and **cohort 2**- Belimumab unexposed (disease control) (See Section 8.5 for

sample size). Participants will be recruited into the two cohorts based on the following inclusion/exclusion criteria:

### 8.2.1. Inclusion/exclusion criteria

*Cohort 1: Belimumab-Exposed group*

Inclusion Criteria

- Eligible subjects will be currently pregnant women diagnosed with SLE who contact the MotherToBaby/OTIS Research Center and who have been exposed to belimumab for any number of days, at any dose, and at any time from 3 months prior to the first day of the LMP up to and including the end of pregnancy.
- Eligible subjects will be currently pregnant women who agree to the conditions and requirements of the study including informed consent, the interview schedule and release of medical records.

Exclusion Criteria*

- Women will not be eligible for Cohort 1 if they first contact the OTIS Research Center after the outcome of pregnancy is known (i.e. the pregnancy has ended prior to enrollment, retrospective enrollment).
- Women will not be eligible for Cohort 1 if results of a diagnostic test are positive for a major structural defect prior to enrollment. However, women who have had any normal or abnormal prenatal screening or diagnostic test prior to enrollment are eligible as long as the test result does not indicate a major structural defect.
- Women will not be eligible for Cohort 1 if they have enrolled in the belimumab study with a previous pregnancy.

**Pregnant women exposed to belimumab who do not meet the exposed cohort inclusion criteria of this study may be followed separately as part of an exposure case series. Information on birth outcomes can be obtained and can be useful when descriptively reviewing the cohort data for any evidence of increased risks for the study outcomes and as such, these women will be invited to enroll in the separate exposure series. With informed consent, data will be collected from maternal interviews and medical records, using the same procedure as the cohort study to the extent possible*

*Cohort 2: Belimumab-Unexposed Disease Comparator Group*

Inclusion Criteria

- Eligible subjects will be currently pregnant women diagnosed with SLE but who were not exposed to belimumab from 3 months prior to LMP or anytime during pregnancy (but may have been exposed to other medications for treatment of SLE during the same time period).
- Eligible subjects will be currently pregnant women who agree to the conditions and requirements of the study including informed consent, the interview schedule and release of medical records.

Exclusion Criteria

- Women who have received treatment with belimumab from 3 months prior to the first day of the LMP up to and including the end of pregnancy but who are not eligible for Cohort 1 will not be eligible for Cohort 2.
- Women will not be eligible for Cohort 2 if they first contact the OTIS Research Center after the outcome of pregnancy is known (i.e. the pregnancy has ended prior to enrollment, retrospective enrollment).
- Women will not be eligible for Cohort 2 if results of a diagnostic test are positive for a major structural defect prior to enrollment. However, women who have had any normal or abnormal prenatal screening or diagnostic test prior to enrollment are eligible as long as the test result does not indicate a major structural defect.
- Women will not be eligible for Cohort 2 who have enrolled in the belimumab study during previous pregnancy.

### 8.2.2. Study conduct

The cohort study will be conducted by investigators at the University of California Research Center for the MotherToBaby/ OTIS. The OTIS organization is a network of university and health department based telephone information centers serving pregnant women and health care providers throughout the U.S. and Canada [Leen-Mitchell, 2000]. These services receive spontaneous telephone inquiries from women who are pregnant or considering pregnancy as well as from health care providers about the safety or risk associated with environmental exposures in pregnancy, including medications. Trained

Teratogen Information Specialists at each site provide appropriate risk assessment and referral for all patient and health care provider callers free of charge. These services also provide a basis for collaborative research such as this study. Thus, individual Teratogen Information Services located throughout the U.S. and Canada will serve as a primary source of referrals not only for belimumab-exposed pregnancies but also for similarly ascertained pregnant women with a diagnosis of SLE but not treated with belimumab.

Other methods of raising awareness about the study are meeting exhibits at professional practice meetings nationally, regionally and locally, direct mail to health care providers, media, social media, and website. Rheumatologists and rheumatology healthcare professionals will be a particular focus of awareness activities. Awareness activities will also be directed to maternal-fetal medicine specialists, obstetricians, primary care physicians (PCP), and other specialists caring for women with SLE.

The US and Canada's belimumab package insert contains information about the belimumab pregnancy exposure registry and encourages healthcare providers to register patients and pregnant women to register themselves by calling the study toll-free number as soon as the pregnancy is known.

In addition, members of the Scientific Advisory Board will be asked to promote recruitment among colleagues. The existing Toll Free number for North American callers currently being utilized by all MotherToBaby Pregnancy Studies and the OTIS Autoimmune Diseases in Pregnancy Project (877-311-8972) will be maintained as a considerable amount of previous publicity for this number will enhance ease of contact for patients to the Registry.

The existing MotherToBaby/OTIS Autoimmune Diseases in Pregnancy Project contact and referral information is available on the website and multiple methods are used to increase awareness through the website (https://mothertobaby.org/pregnancy-studies/), social media and print advertising. The FDA website (http://www.fda.gov/womens/registries/default.htm) lists the MotherToBaby/OTIS Pregnancy Studies and will have this Registry added to their listing. The study will also be listed on ClinicalTrials.gov.

This information will also be made available 1) in the prescribing information (package insert) for belimumab and other product literature and promotional materials, and 2) via a link from the GSK website. Additional venues for publicizing the Registry include: 1) linking the Registry website to other specialty provider and maternal health interest websites, 2) posting notices in appropriate journals or patient advocacy publications, and 3) later, presenting Registry data at specialty provider, and obstetrics-related scientific and clinical meetings. In addition, the Registry will enlist the aid of the U.S. Food and Drug Adminisation (FDA), the U.S. Centers for Disease Control and Prevention (CDC), and other relevant organizations in facilitating patient recruitment, and the Sponsor will also provide information about the Registry at appropriate professional meetings. Additional venues for publicizing the Registry include advocacy groups and patient support networks. The Sponsor may facilitate awareness among prescribers through Medical Science Liaisons.

The Sponsor will encourage exposed women or their Healthcare Providers to contact the Registry directly.

Women who are interested in hearing more about the study will be referred to or will self-refer themselves to the MotherToBaby/OTIS Research Center for more information. Referrals may be by the woman's healthcare provider or by the MotherToBaby/OTIS service that the woman contacts directly. Those women who are interested and meet the study criteria as described in Section 8.2 will be invited to enroll. Women who agree to enroll will complete the oral consent process over the telephone and will then complete the initial telephone interview. Depending on the gestational timing of enrollment, subsequent telephone interviews will be conducted according to the Schedule shown in Table 5 Section 8.6.3. Follow up interviews will be conducted by telephone, and medical records for both the women and infant will be obtained and abstracted for information to validate exposures and outcomes.

The participants will reside anywhere in the U.S. or Canada. By definition, the study participants are all female, as this is a pregnancy study. The age of participants is expected to be between 18 and 45 years; however, women under the age of 18 years may enroll with parent/guardian consent, and women over the age of 45 years may also enroll.

Upon initiation of recruitment, the study is expected to continue recruitment for five years. Infant follow-up will continue for one year after the last live birth following recruitment of the last participant.

**Table 1 Recruitment Timetable**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Cohort 1<br>Belimumab exposed group | 40 | 43 | 48 | 47 | 42 |
| Cohort 2<br>Disease comparison group | --* | 50 | 50 | 50 | 50 |
| Exposure Case-Series | 10 | 10 | 10 | 10 | 10 |
| *Year 1: Will assess feasibility of collecting exposed group; once n=40 is attained, recruitment of comparison group will begin | | | | | |

## 8.3. Variables

### 8.3.1. Exposure definitions

*Belimumab-exposed cohort*: Exposure is defined as any dose of belimumab for any length of time from 3 months prior to the first day of the LMP (i.e., a period of approximately 5 belimumab terminal half-lives) through the end of pregnancy, as reported by the mother and validated through medical record review (mean termination elimination half-life of 8.5 to 14.1 days, [Furie, 2008]). Belimumab exposure will be further categorized by earliest trimester of exposure (definition from https://www.womenshealth.gov/pregnancy/youre-pregnant-now-what/stages-pregnancy; https://www.ucsfhealth.org/conditions/pregnancy/trimesters). For this study, pre-conception exposure is defined as between 3 months prior to LMP to the first day of the LMP, first trimester exposure is defined as any dose from1st day of LMP and up to 13 weeks after 1st day of LMP; second trimester is defined as >13 weeks through 26 weeks

after 1st day of LMP, and third trimester is defined as >26 weeks after 1st day of LMP. Details of varying levels of exposure and timing will be included in the Statistical Analysis Plan (SAP).

When evaluating the primary outcome of major birth defects, exposure will be defined as yes/no in either the preconception and/or first trimester of pregnancy for major birth defects as the primary outcome. However, exposure to belimumab in the second (>13 weeks through 26 weeks after 1st day of LMP) and third trimester (>26 weeks after 1st day of LMP), will be considered for those selected major birth defects that are potentially biologically plausibly related to later pregnancy exposures, e.g., craniosynostosis [Jones, 2013]. For spontaneous abortion, the exposure is defined as yes/no in the 3 months prior to LMP and/or any time in pregnancy prior to 20 weeks of gestation, for preterm delivery, the exposure is defined as yes/no in the 3 months prior to LMP and/or any time in pregnancy prior to 37 weeks, for minor birth defects, the exposure is defined as yes/no from 3 months prior to LMP through the end of the first trimester, and for the other secondary outcomes, exposure is defined as yes/no anytime in pregnancy (from 3 months prior to LMP [as defined in Section 8.3.2] to pregnancy outcome).

Gestational age is determined by an algorithm using best available information. If the first day of LMP and cycle length is known, and ultrasound measures of dating are not discrepant according to standard conventions depending on the timing of the ultrasound, the menstrual period dating will be used to calculate gestational age. If the menstrual period dating is uncertain or unknown, and an ultrasound is available, the earliest (and therefore more precise) available ultrasound dating will be used. In the event of absence of any information on dating, the delivery record best estimate of gestational age will be used.

### 8.3.2. Outcome definitions

Outcome definitions and details are listed in Table 2.

**Table 2 Primary and Secondary Outcome Definitions**

| Outcome | General definition | Denominator | Pregnancy involving multiples | Outcome assessment | Exposure time | Endpoints |
|---|---|---|---|---|---|---|
| **Pregnancy Outcome (Primary)** | | | | | | |
| ***Major Birth Defect***[2] | Defined and classified using the CDC coding manual [CDC 2017], reported by the mother and validated through the medical record. The CDC coding manual is utilized to classify defects reported through the ongoing population-based Metropolitan Atlanta Congenital Defects Program (MACDP) and is based on agreed-upon criteria by CDC investigators for major birth defects regardless of etiology. Infant medical records are abstracted and reviewed by the study research team leaders. | Pregnancies ending in live births | **Included** counted as one case if at least one infant has a birth defect. | At birth or prior [may also be detected up to 1 year of age] | 3 months prior to LMP and/or first trimester | **Primary analysis (among pregnancies with at least one live births)**<br>**Cohort 1:** At least one malformed infant in an individual pregnancy among pregnancies ending in at least one live birth with exposure to 3 months prior to LMP and/or 1st trimester<br><br>**Cohort 2:** At least one malformed infant in an individual pregnancy among pregnancies ending in at least one live birth with no exposure to belimumab any time in pregnancy[3]<br><br>**Secondary analysis (among all pregnancies excluding lost-to-follow up)**<br>**Cohort 1:** At least one malformed infant or fetus in an individual pregnancy among pregnancies ending in at least one live birth with exposure to belimumab 3 months prior to LMP and/or 1st trimester<br><br>**Cohort 2:** At least one malformed infant or fetus in an individual pregnancy among pregnancies ending in at least one live birth with no exposure to belimumab any time in pregnancy[3] |

| Outcome | General definition | Denominator | Pregnancy involving multiples | Outcome assessment | Exposure time | Endpoints |
|---|---|---|---|---|---|---|
| **Pregnancy Outcomes (Secondary)** | | | | | | |
| ***Spontaneous abortion (SAB)*** | Defined as spontaneous pregnancy loss prior to 20 weeks' gestation (including ectopic/molar pregnancy). In this study, since women enroll after recognition of pregnancy, SABs are only identified after enrollment in clinically recognized pregnancies. This outcome is reported by the mother and validated through the medical record, where available. | Pregnancies | **Included** counted as one case if all multiple pregnancies ended in SAB. Pregnancy is counted as a live birth outcome if at least one pregnancy resulted in a live-born infant | Up to 20 weeks gestation | Prior to 20 weeks gestation | **Cohort 1:** SAB among all pregnancies enrolled in the study prior to 20 weeks' gestation with exposure at any time in pregnancy[3] prior to 20 weeks and with at least 1 follow-up data collection point after enrollment date<br><br>**Cohort 2:** SAB among all pregnancies enrolled in the study prior to 20 weeks' gestation with no exposure at any time in pregnancy[3], with at least 1 follow-up data collection point after enrollment date |
| ***Stillbirth*** | Defined as a fetal death that occurs ≥ 20 weeks' gestation. | Pregnancies | **Included** counted as one case if all multiple pregnancies ended in stillbirth. Pregnancy is counted as a live birth outcome if at least one pregnancy resulted in a live-born infant | At birth | 3 months prior to LMP and/or any time in pregnancy[3] prior to outcome | **Cohort 1**: Stillbirths among all pregnancies[1] with exposure at any time in pregnancy[3];<br><br>**Cohort 2**: Stillbirths among all pregnancies[1] with no exposure at any time in pregnancy[3]; |

| Outcome | General definition | Denominator | Pregnancy involving multiples | Outcome assessment | Exposure time | Endpoints |
|---|---|---|---|---|---|---|
| ***Elective Termination*** | Defined as deliberate termination of pregnancy at any time in gestation by surgical or medical means. Reasons for elective abortions are captured and are classified as due to medical reasons or social reasons. | Pregnancies | **Included** counted as one case if all multiple pregnancies ended in elective termination. Pregnancy is counted as a live birth outcome if at least one pregnancy resulted in a live-born infant | During pregnancy | 3 months prior to LMP and/or at any time in pregnancy[3] prior to outcome | **Cohort 1**: Elective termination among all pregnancies[1] with exposure at any time in pregnancy[3];<br><br>**Cohort 2**: Elective termination among all pregnancies[1] with no exposure at any time in pregnancy[3]; |
| ***Preterm Delivery*** | Defined as a spontaneous or induced delivery at <37 gestational weeks, reported by the mother and validated through the medical record. Please refer to Section 8.3.1 for further description of the method for defining gestational age and therefore preterm birth. | Pregnancies ending in live births | **Excluded** due to inherent higher risk of preterm birth in multiple | At birth | 3 months prior to LMP and/or at any time in pregnancy[3] prior to 37 weeks | **Cohort 1:** Preterm delivery among pregnancies enrolled prior to 37 weeks' gestation and ending in at least one live birth, with exposure at any time in pregnancy[3] prior to 37 weeks;<br><br>**Cohort 2:** Preterm delivery among pregnancies enrolled prior to 37 weeks' gestation and ending in at least one live birth, with no exposure at any time in pregnancy[3]; |

| Outcome | General definition | Denominator | Pregnancy involving multiples | Outcome assessment | Exposure time | Endpoints |
|---|---|---|---|---|---|---|
| **Infant Outcomes (Secondary)** | | | | | | |
| ***Small for Gestational Age (SGA) Infants*** | Defined as live born infants who are ≤10th centile on birth weight for infant sex and gestational age will be considered small for gestational age. The U.S. Centers for Disease Control and Prevention (NCHS) [CDC, 2000] growth charts will be used for full term infants, and the Olsen growth charts will be used for preterm infants [Olsen, 2010]. The outcome of birthweight is reported by the mother and validated through the medical record. | live born infants | **Excluded** due to inherent higher risk of reduced birth size in multiples | At birth | 3 months prior to LMP and/or at any time in pregnancy[3] | **Cohort 1:** SGA among live born infants with exposure at any time in pregnancy[3];<br><br>**Cohort 2:** SGA among live born infants, with no exposure at any time in pregnancy[3] |
| ***Minor birth defect pattern*** | A minor birth defect is defined as a defect that has neither cosmetic nor functional significance to the child and as itemized on the study-related dysmorphology examination form (Jones, 2013). Minor defect pattern will be defined using the following two steps: 1) identify infants with at least 3 minor structural defects of any type in the belimumab-exposed group and 2) from among infants with at least 3 minor structural defects in the belimumab-exposed group, identify any 2 or more unrelated infants with the same 3 specific minor structural defects. The prevalence of each specific pattern or patterns, if any, that are identified in the belimumab-exposed infants will be identified in the unexposed SLE comparator group. As an example, if 2 infants in Cohort 1 had the following | Live born infants | **Included** each counted separately for definition 1<br><br>However, in the analysis of the second definition, only one infant from a twin or higher order multiple pregnancy can be qualified as a child with the same pattern of minor structural defects, due to lack of independence for this outcome between related individuals. | Any time after birth | 3 months prior to LMP and/or anytime in the 1st trimester | **1) Infant with at least 3 minor defects of any type:**<br>**Cohort 1**: Infants ≥ 3 minor birth defects of any type identified up to among live born infants who received a dysmorphological examination, with exposure at any time in pregnancy[3]<br>**Cohort 2**: Infants ≥ 3 minor birth defects of any type identified up to among live born infants who received a dysmorphological examination, with no exposure at any time in pregnancy[3];<br><br>**2) Infants with the same 3 minor defect patterns:**<br>**Cohort 1**: Infants with the same pattern of 3 minor defects identified up to among live born infants with ≥ 3 minor birth defects of any type identified any time in pregnancy[3];<br>**Cohort 2**: Infants with the same pattern of 3 minor defects identified up to among live born |

| Outcome | General definition | Denominator | Pregnancy involving multiples | Outcome assessment | Exposure time | Endpoints |
|---|---|---|---|---|---|---|
| | minor structural defects: "hair pattern unruly", "prominent nasal bridge", and "clinodactyly 5th finger bilateral", this would constitute one specific pattern of minor structural defects. For each specific pattern identified in Cohort 1, infants in Cohorts 2 who have the same specific pattern(s) are selected to comprise the numerator for those cohorts. In infants who have more than one specific patterns of at least 3 minor structural defects, each specific pattern will qualify as its own endpoint; therefore, the infant would be counted more than once. | | | | | infants, with ≥ 3 minor birth defects of any type identified, with no exposure at any time in pregnancy[3]; |
| **Post-natal growth deficiency** | Defined as postnatal size at approximately 1 year of age (weight, length or head circumference) less than or equal to the 10th percentile for sex and age using National Center for Health Statistics (NCHS) pediatric growth curves, and adjusted postnatal age for premature infants if the postnatal measurement is obtained at less than 1 year of age. [CDC, 2000]. | Live born infants | **Excluded** due to inherent higher risk of reduced birth size in multiple | From birth up to 1 year of age | 3months prior to LMP and/or at any time in pregnancy[3] | **Cohort 1:** Post-natal growth deficiency identified up to 1 year of age among live born infants with exposure at any time in pregnancy[3]<br><br>**Cohort 2:** Post-natal growth deficiency identified up to 1 year of age among live born infants, with no exposure at any time in pregnancy[3] |
| ***Developmental concerns*** | Defined as an abnormal score within the scoring guidelines of the Ages and Stages Questionnaire (ASQ) (Squires, 2009). The ASQ is administered at 12 months of age as a screening tool for developmental milestones by parent report. The ASQ-3 will be sent electronically to the participant or, if the participant prefers, a hard copy questionnaire will be mailed for completion. | Live born infants | **Included** each counted separately | At 1 year of age | 3months prior to LMP and/or at any time in pregnancy[3] | **Cohort 1:**Developmental concerns identified at 1 year of age among live born infants, with pregnancy exposure at any time in pregnancy[3];<br><br>**Cohort 2**: Developmental concerns identified at 1 year of age among live born infants, with no exposure at any time in pregnancy[3] |

| Outcome | General definition | Denominator | Pregnancy involving multiples | Outcome assessment | Exposure time | Endpoints |
|---|---|---|---|---|---|---|
| ***Serious infections up to one year of age:*** | Defined infections requiring hospitalization identified in live born infants up to one year of age | Live born infants | **Included** each counted separately | From birth up to 1 year of age | 3 months prior to LMP and/or at any time in pregnancy[3] | **Cohort 1:**Serious infections identified up to 1 year of age among live born infants, with pregnancy exposure at any time in pregnancy[3];<br><br>**Cohort 2**: Serious infections identified up to 1 year of age among live born infants, with no exposure at any time in pregnancy[3] |

[1]Pregnancy outcomes include ending in live births, spontaneous abortion, elective termination, or stillbirth

[2]Exposure in the 2nd and 3rd trimester will be considered for those selected major birth defects that are potentially biologically plausibly related to later pregnancy exposures, e.g., craniosynostosis

[3]Any time pregnancy defined as any exposure from 3 months prior to LMP through the end of pregnancy (see Section 8.3.1 for details)

### 8.3.3. Confounders and effect modifiers

The potential confounders/effect modifiers listed below will be considered in multivariable analyses, where possible, as well as others that are relevant to each of the study outcomes:

- Maternal and paternal age
- Previous pregnancy history: gravidity and parity, previous spontaneous abortions and elective terminations
- Maternal and paternal race/ethnicity, education, occupation, socioeconomic status
- Pre-pregnancy body mass index
- Previous preterm delivery
- Previous child with a birth defect
- Maternal conditions: e.g., depression, diabetes
- Maternal exposures: gestational timing and dose of all over-the-counter and prescription medications, including all medications for the treatment of SLE used during pregnancy; vitamin and mineral supplements, herbal products; illnesses; fever; vaccinations
- Prenatal testing: ultrasound and other prenatal tests; timing in gestation and results
- Pregnancy complications: e.g., pregnancy induced hypertension, gestational diabetes, prolonged labor (definitions included in Section 14 Glossary)
- Maternal lifestyle habits: cigarette smoking, alcohol consumption and illicit drug use
- SLE disease severity assessment (see ANNEX 1 [Section 15.1] for details)
- Relevant lab values where available (e.g., CBC with differential, urinalysis: protein, red blood cell (RBC), white blood cell (WBC), casts, urine protein:creatinine ratio, dsDNA antibody, anti-phospholipids C3 and C4)
- Infant complications: e.g., hospitalizations, congenital heart block,
- Relevant pediatric exposure: any vaccines administered, infections requiring hospitalization in first year of life, breastfeeding status

Methods for identifying and controlling for these confounders and/or effect modifiers are described in Section 8.7.1. The SAP will provide greater detail on the definitions of, the identification of and the controlling for confounders and/or effect modifiers.

## 8.4. Data sources

*Maternal Interviews*: In the two cohort study groups, as well as the case-series, data are collected by semi-structured maternal telephone interview on two to four occasions (depending on gestation age at enrollment) during and shortly after completion of pregnancy (please see Table 3 and Table 6 for specific timing and content of interviews).

The interviews include data on exposure timing, dose, and duration for all medications, including belimumab, taken anytime in pregnancy as well as data on a wide variety of confounders (See Section 8.3.3).

For women exposed to belimumab or other medications used for the treatment of SLE, information on disease severity is obtained directly from the mother at every interview (intake/enrollment and 32 week's gestation and outcome assessment maternal telephone interviews) (see ANNEX 1 [Section 15.1] for information on patient disease severity assessments). At the conclusion of pregnancy, regardless of the outcome, participants are interviewed about the outcome including presence or absence of birth defects, pregnancy and infant complications and infant size.

*Medical Records:* Mothers are asked to release medical records to the study investigators from their obstetrician or other obstetric provider, specialty care provider such as their rheumatologist/nephrologist, hospital of delivery, pediatrician, and any other health care provider involved in the pregnancy. These records are abstracted and used to validate pregnancy and infant outcomes and when necessary to provide details regarding timing or dose of belimumab and other medications used for the treatment of SLE in the absence of complete information from maternal report as well as validating any potential confounders/effect modifiers. Pre-defined definitions for each of the study outcomes are used for classification (Table 2).

Validation of classification of major birth defects, the primary outcome, is conducted periodically and before each annual and final study reports by the Co-Investigator and dysmorphologist, who is an expert in diagnosing birth defects.

Other data sources used within the study include Ages and Stages Questionnaire (ASQ-3) self-administered by mother and the dysmorphological physical examination for infant outcomes assessments

**Table 3 Variables collected per cohort**

| Variable | Cohort 1 Belimumab-exposed | Cohort 2 Disease comparison | Case-Series Belimumab-exposed (non-cohort) | Data Collection Time Period |
|---|---|---|---|---|
| ***Maternal Interviews***[6] | | | | |
| Belimumab exposure timing | √ | | √ | At every interview |
| Belimumab dose | √ | | √ | At every interview |
| Belimumab duration | √ | | √ | At every interview |
| Pregnancy Outcomes | | | | |
| Any birth defects | √ | √ | √ | At every interview |
| Other pregnancy outcomes[4] | √ | √ | √ | At outcome interview |
| Infant Outcomes (up to 1 year of age) | | | | |
| Infant size | √ | √ | √ | At outcome interview |
| Serious infections | √ | √ | √ | At outcome interview |
| Developmental concerns[8] | √ | √ | √ | 1 year of age |
| Potential confounders/effect modifiers | | | | |
| Maternal/paternal characteristics | √ | √ | √ | At enrollment interview |
| Self-reported disease severity | √ | √ | √ | At every interview |
| Previous pregnancy and delivery birth defect history | √ | √ | √ | At enrollment interview |
| Maternal conditions | √ | √ | √ | At every interview |
| Other maternal exposures/concomitant medications[1] | √ | √ | √ | At every interview |
| Maternal lifestyle habits | √ | √ | √ | At every interview |
| Prenatal testing | √ | √ | √ | At every interview |
| Pregnancy complications | √ | √ | √ | At every interview |
| Infant complications and pediatric exposures | √ | √ | √ | At outcome interview |
| ***Medical Record Abstraction***[2,7] | | | | |
| SLE diagnosis validation[5] | √ | √ | √ | Medical history |
| Pregnancy validation | √ | √ | √ | Medical history |
| Belimumab Exposure | | | | |
| Exposure timing, dose, duration validation | √ | | √ | Preconception to pregnancy outcome |
| Pregnancy Outcomes | | | | |
| Major birth defects[3,9] | √ | √ | √ | LMP to infant 1 year of age |
| Other pregnancy outcome validation[4] | √ | √ | √ | LMP to pregnancy outcome |
| Infant Outcomes (up to 1 year of age) | | | | |
| Birth and postnatal growth | √ | √ | √ | Birth to 1 year of age |

| Variable | Cohort 1 Belimumab-exposed | Cohort 2 Disease comparison | Case-Series Belimumab-exposed (non-cohort) | Data Collection Time Period |
|---|---|---|---|---|
| Serious infections | √ | √ | √ | Birth to 1 year of age |
| Minor birth defect patterns[3,9] | √ | √ | √ | Birth to time of dysmorphology examination |
| Potential confounders/effect modifiers | | | | |
| Clinically assessed disease severity | √ | √ | √ | Preconception to pregnancy outcome dependent on last clinical assessment |
| Previous pregnancy, delivery birth defect history validation | √ | √ | √ | Medical history |
| Maternal conditions validation | √ | √ | √ | Medical history |
| Maternal exposure/concomitant medications[1] validation | √ | √ | √ | Preconception to pregnancy outcome or within 2 years of LMP for specific exposures |
| Prenatal testing validation | √ | √ | √ | LMP to pregnancy outcome |
| Infant complications and pediatric exposures | √ | √ | √ | Birth to 1 year of age |
| Infant vaccination status | √ | √ | | Birth to 1 year of age |
| Birth and postnatal growth | √ | √ | √ | Birth to 1 year of age |
| Serious infections up to 1 year of age | √ | √ | √ | Birth to 1 year of age |

[1] For cohorts 1& 2 primarily medications used for the treatment of SLE will be assessed.
[2] Information will be dependent on the completeness of the medical record
[3]Performed periodically and before each annual and final study reports
[4] Includes preterm delivery, spontaneous abortion, elective termination, stillbirth, small for gestational age
[5] including clinical manifestations such as lupus nephritis if available
[6] Maternal interviews: can be up to 4 interviews, depending on gestational age at enroll
ment and include: enrollment interview (any time in pregnancy), interim interview I (20-22 weeks gestations), interim interview II (32-34 weeks gestation), and pregnancy outcome interview (0-6 weeks post-delivery)
[7] Medical record review will occur at 0-12 months post-delivery for pregnancy information and 1 year post-delivery for infant information
[8] The ASQ-3 will be sent electronically to the participant or, if the participant prefers, a hard copy questionnaire will be mailed for completion.
[9] Data also collected from the study dysmorphological examination

## 8.5. Study size

The proposed sample sizes in each of the study groups are as follows:

- 200 women exposed to belimumab at any time from 3 months prior to the first day of LMP through the end of pregnancy
- 200 women with SLE, unexposed to belimumab

An enrollment of 200 participants in each of the cohort groups is planned over 5 years. Based on previous experience with the MotherToBaby/OTIS Autoimmune Diseases in Pregnancy Project, the expected proportion of women to enroll in first trimester is approximately 70% [Chambers, 2019a]. It is estimated that participants will be an average of 7-10 weeks post-LMP at the time of enrollment. Given this mean gestational timing at enrollment, the anticipated live-birth rate is 85%, which includes a spontaneous abortion and elective abortion rate of 10% [Wilcox, 1988; Zinaman, 1996; Kanmaz, 2019; Chambers, 2019a] and an estimated lost to follow-up rate of 5% [Chambers, 2018], this will result in 170 pregnancies with at least one live born infant in each cohort at the end of recruitment. As a conservative estimate, the power calculations were also conducted assuming a live-birth rate of 80%, which includes a spontaneous abortion and elective abortion rate of 15% [Chambers, 2016], and an estimated lost to follow-up rate of 5%. This conservative estimate will result in 160 pregnancies with at least one live born infant in each cohort at the end of recruitment.

This study is designed to serve as an early warning system to identify a previously unrecognized major teratogen by identifying major birth defects in infants of exposed mothers. For less potent teratogens or for drugs and biological products that cause other adverse pregnancy outcomes, the study can function as a signal detection study and generate hypotheses that can be tested in other studies using other methods that may be better powered to assess these outcomes (FDA, 2019).

Table 4 gives the minimum detectable effect sizes with 80% power [two-sided significance level 0.05]) for the primary outcome of major birth defects. Table 4 includes

varying expected live births in each cohort, using varying rates of SAB/elective terminations and includes varying background rates of major birth defects, based on existing literature on pregnant women with SLE [Vinet, 2012; Gladman, 2010]. As a reference, the effect size has also been calculated based on the general population background rate of major birth defects of 2.8% in the Atlanta metropolitan area [CDC, 2017].

**Table 4 Risk estimates for belimumab-exposed pregnancies relative to the primary comparison group for the primary outcome; all estimates use an α-level of 0.05 and power of 0.8 (80%).**

| Outcome | N in Each Group* | Target Enrolled N in Each Group | Rate in Comparison Group** | Relative Risk*** |
|---|---|---|---|---|
| **Using background rates of primary outcome within SLE population** | | | | |
| Major birth defects | 160 | 200 | 13%[a] | 1.9 |
| Major birth defects | 160 | 200 | 5%[b] | 2.8 |
| Major birth defects | 170 | 200 | 13%[a] | 1.9 |
| Major birth defects | 170 | 200 | 5%[b] | 2.7 |
| **Using background rates of primary outcome within general population as reference** | | | | |
| Major birth defects | 160 | 200 | 3%[c] | 3.5 |
| Major birth defects | 170 | 200 | 3%[c] | 3.4 |

N= number of pregnancies with at least one live born infant
*Sample size for the first two rows of the table allows for spontaneous abortion and elective abortion rate of 15% (Chambers, 2016) and lost to follow-up rate of 5%; sample size (Chambers, 2018) for the following two rows of the table allows for spontaneous abortion and elective abortion rate of 10% (Wilcox, 1988; Zinaman, 1996; Kanmaz, 2019; Chambers, 2019a), and lost to follow-up rate of 5%.
**Sample size for major birth defects based on varying prevalence in the SLE comparison group. The 13% is an upper end estimate from Vinet et al, the 5% is a median estimate from Gladman, 2020 and the 3% is the estimate from CDC); sample size based on prevalence within the general population , 2017). Power calculations performed in open-sourced statistical programming language R software.
*** Minimum relative risk (RR) detectable with 80% power.
[a]Vinet, 2012; [b]Gladman, 2010; [c]CDC, 2017

Group sample sizes of 160 in each group achieve 80% power to detect a ratio of 1.9 to 2.8 when the null-hypothesized ratio is 1.0 and when background rates of major birth defects in pregnant women with SLE are used. The test statistic used is the two-sided Score test [Farrington, 1990]. The significance level of the test was targeted at 0.050. For the secondary outcome of spontaneous abortion, allowing for an elective abortion rate of 5% and a lost to follow-up rate of 5%, an estimated 180 pregnancies are expected in each cohort at the end of recruitment. Group sample sizes of 180 in each group achieve

80% power to detect a ratio of 2.1 when the null hypothesized ratio is 1.0 and when a background rate of spontaneous abortion of 10% is used. The test statistic used is the two-sided Score test [Farrington, 1990]. The significance level of the test was targeted at 0.050.

## 8.6. Data management

Maternal interviews are conducted at enrollment and in each trimester thereafter, depending on the gestational age at which the mother enrolls. An additional outcome interview is conducted by telephone after the end of pregnancy, typically this occurs within 6 weeks but could be up to one year after. These interviews are conducted by telephone and typically take between 30 minutes and 1 hour to complete. The interviews are semi-structured and follow interview data collection forms to ensure that all study questions are addressed. Data from each interview form is entered into the study database at the end of the interview by the same person who conducted the interview. Medical records are requested from the hospital of delivery (maternal and neonatal information), obstetric provider (maternal information), pediatrician (neonatal/infant) and any specialty physician (maternal and neonatal/infant information). When records are received and catalogued, data is abstracted by trained personnel from each record using a standard abstraction form and entered into the study database. Hard copies or electronic copies of all study forms and medical records are retained in the OTIS Research Center at the University of California, San Diego. Several logic checks are built into the study database. In addition, all data entry is validated for a series of predefined critical variables and a random subset are validated for non-critical variables. Access to the database is controlled by password with administrative level access required for certain operations. Hard copies or electronic copies of patient files and subject signed consent forms will be kept in locked file rooms, locked cabinets or locked electronic drives under the supervision of the study investigators.

### 8.6.1. Data handling conventions

Major birth defects are classified using the CDC coding manual [CDC, 2017] by the Study dysmorphologist. All defect classifications are reviewed by the Study

Investigators. All prenatal exposures to medications and vaccines are coded using the Slone Drug Dictionary (http://sites.bu.edu/slone-drug-dictionary/).

Twins or higher order multiples are handled as one pregnancy outcome. For example, if the pregnancy ends in at least one live born infant, the outcome is considered a live born outcome. If either or both twins have a major birth defect, the outcome is considered one major birth defect outcome. Twins are excluded from analyses of preterm delivery and SGA infants.

Lost-to-follow-up status is designated if a participant withdraws from the study, or if the study staff are unable to make contact with the study participant within 12 months of the estimated end of pregnancy in order to obtain outcome information.

Coding of outcomes is performed by the study staff using the definitions provided in the protocol. The primary source of information on exposure and outcome is the participant. Validation of study outcomes is performed using medical records. In the case of discrepancies in the two sources of report, the participant is recontacted to determine if the discrepancy can be resolved, and a Standard Operating Procedure (SOP) for adjudicating these decisions has been developed.

Missing values for the critical data for OTIS studies are typically very few and nearly always less than 10%. Complete case analysis is planned and there is generally no need to include imputation strategies; however, depending on the prevalence of missingness, sensitivity analyses will be conducted. These will be documented in the SAP.

### 8.6.2. Resourcing needs

Not applicable.

### 8.6.3. Timings of Assessment during follow-up

**Table 5 Timing of Cohort Enrollment, Interviews, 2 Medical Records**

| | Any Time in Pregnancy | 20-22 Weeks' Gestation | 32-34 Weeks' Gestation | 0-6 Weeks Post-Delivery | 0-12 Months Post-Delivery | 1 Year Post-Delivery |
|---|---|---|---|---|---|---|
| Referral | √ | | | | | |
| Enrollment and Consent | √ | | | | | |
| Enrollment Interview | √ | | | | | |
| Interim Interview I | | √ | | | | |
| Interim Interview II | | | √ | | | |
| Pregnancy Outcome Interview and Request for Medical Records* | | | | √ | | |
| Pregnancy Medical Record Review | | | | | √ | |
| Pediatric 1-Year Medical Records Request and Review | | | | | | √ |
| Pediatric 1-Year ASQ | | | | | | √ |

*Contact earlier if pregnancy outcome occurs earlier

## 8.7. Data analysis

### 8.7.1. Essential analysis

A stepwise approach will be used for the analysis: The initial analysis will be descriptive and unadjusted. Where numbers permit, multivariable analyses will be conducted for the primary and secondary analyses to adjust for possible confounders.

***Statistical methods*:**

A detailed SAP will be prepared and finalized prior to the conduct of any study analysis.

Patient characteristics will be summarized within each cohort for the interim and final reports.

Table 6 summarizes the exposure window for each outcome.

**Table 6 Summary of Exposure Window for Each Outcome**

| Outcome | Exposure Window |
|---|---|
| Major Birth Defects | 3 months prior to LMP to the end of the 1st trimester |
| Minor Birth Defects | 3 months prior to LMP to the end of the 1st trimester |
| Spontaneous Abortion/Miscarriage | 3 months prior to LMP to prior to 20.0 weeks' gestation |
| Preterm Delivery | 3 months prior to LMP to prior to 37.0 weeks' gestation |
| Other Outcomes | 3 months prior to LMP to the end of the pregnancy |

**For the primary endpoint,** the exposure of interest is belimumab exposure in the pre-conception/first trimester period. For this study, this exposure is defined as any dose from 3 months prior to the 1st day of LMP and up to 13 weeks after the1st day of the LMP. The primary comparison will be on the rate of major birth defects between Cohort 1 and Cohort 2 among pregnancies resulting in at least one live born infant. A point estimate of the crude (i.e. unadjusted) RR of Cohort 1 versus Cohort 2, as well as its 95% confidence intervals (CIs) will be computed.

The comparison will also be carried out within each of two strata, according to whether the woman had prenatal diagnostic testing, such as level II ultrasound, amniocentesis or chorionic villus sampling, prior to enrollment in the study or not.

The same analysis will be repeated using the second numerator and denominator encompassing pregnancies ending in at least one live births, stillbirth, spontaneous abortion or elective termination, but excluding those lost-to-follow-up.

Due to the observational nature of the study, the above crude estimate of RR will be further adjusted for potential confounders, provided that there are sufficient number of events. A complete list of potential confounders will be provided in a separate table for each outcome prior to the final analysis, based on scientific knowledge including literature review. In addition, all of the following three criteria will be applied in

accordance with the definition of confounders, and variables will be considered in a step-wise approach where any of these criteria are met: 1) by assessing each considered variable in a logistic regression model containing exposure and the outcome to determine if inclusion of that single covariate changes the estimate of the odds ratio for exposure by 10% or more; 2) standardized mean differences (SMD) greater than 0.1; 3) association with the outcome with p-value <0.2 in the unexposed group. Care will be taken not to include those variables that are strongly associated with the exposure but only weakly associated with the outcome.

The confounders identified above may be used to build the propensity score (PS) for exposure [Rosenbaum, 2002]. R package 'twang' or similar R package available at the time of analysis will be used for this purpose, following which SMD will be used to check the balance of the covariates between the cohorts.

The primary analysis will be performed with inverse probability weighting (IPW) using the propensity score. In the IPW approach, we will use stabilized weights that are further trimmed to be between 0.1 and 10 if necessary [Peter, 2015]. The robust sandwich variance estimator will be used following the IPW approach.

A secondary analysis will be conducted using outcome regression, i.e. a logistic regression model will be fitted with major structural defect (Y) as outcome, and exposure (A) and propensity score (L) as regressors. Standardization will be performed to obtain the estimated causal risk ratio [Hernán, 2019], which has the interpretation as the marginal or population averaged risk ratio. The CIs are obtained by 10,000 bootstraps.

**For the secondary endpoints**

The ideal pregnancy cohort would enroll women at conception, before any outcome, and then follow them for years after delivery. However, this is unrealistic for logistical reasons. Therefore, outcomes that must account for gestational age at enrollment (e.g. SAB) will have left truncation and right censoring. Left truncation occurs because participants enroll after conception and, therefore, after some outcomes may have already occurred. Right censoring occurs when there are enrolled pregnancies with unknown

outcomes due to lost to follow-up, pregnancy miscarriages, or terminations or stillbirths without fetal autopsy. Left truncation (late enrollment) may underestimate the risk of early pregnancy events (e.g., miscarriages, maternal death). Differences in gestational age at enrollment between exposed and reference groups could lead to biased relative risk estimates if the risk varies with gestational age. To prevent this bias, the most useful approach is to enroll subjects as early in their pregnancy as possible before outcomes can be expected and to begin follow-up of exposed and unexposed pregnancies at comparable gestational ages.

Specifically, the analysis of SAB and stillbirths is complicated by left truncation in the data, i.e., women enter the study at arbitrary times in gestation, and analyses of these outcomes must account for gestational age at enrollment. Only those women who are enrolled prior to 20.0 weeks of gestation are eligible for the analysis of SAB. Since they are not followed from gestational age zero, survival analysis methods will be used to handle left truncation, measuring time relative to enrollment, as well as right-censoring when a subject is lost-to-follow-up prior to 20.0 weeks' gestation. Left-truncated Kaplan-Meier estimate at 20.0 weeks' gestation will be used to estimate the spontaneous abortion rate in each of the cohorts with 95% CIs [Tsai, 1987]. The Cox proportional hazards regression models incorporating left truncation will be used to estimate the hazard ratio (HR) and 95% CIs of both cohorts. The individual group hazards and 95% CIs will also be presented. Stillbirth will be analyzed with a similar method.

To account for potential confounding, propensity score methods described above will be applied. In particular, regression adjustment will be used with the Cox model to obtain the adjusted HR.

The analysis of preterm delivery can also be complicated by left truncation in the data, i.e., women enter the study at arbitrary times in gestation. Only those women who are enrolled prior to 37.0 weeks of gestation are eligible for the analysis of preterm delivery. These data will be analyzed similarly to spontaneous abortion as described above using survival analysis methods, to handle possible left truncation and right-censoring.

Endpoints relevant to SGA at birth and postnatal growth deficiency at about 1 year of age in weight, height and head circumference (excluding multiple births) are all binary endpoints. The analysis of each of these outcomes will be similar to the analysis of the primary outcome.

Multiple births will be included in the analyses of minor structural defects, developmental concerns and serious infections. The outcome variables thus contain likely correlated data, and the generalized estimating equations (GEE) approach will be used to estimate the crude RR with 95% CI. The causal effect will be estimated similar to the primary outcome, but in place of logistic regression it will be GEE with the logistic link function. The CIs are obtained by 10,000 bootstraps, where the mothers (not infants) will be resampled with replacement.

### 8.7.2. Exploratory/Sensitivity analyses

For the primary outcome of major structural birth defects,

- exploratory analyses addressing potential effect modifiers such as disease severity will be conducted. Specifically, confounder adjustment might be carried out both including and excluding these disease severity measures;

- sub-analyses using graphical presentation based on gestational timing as well as dose of exposure to belimumab will be performed.

- a sensitivity analysis will be performed excluding those defects thought to be of chromosomal or genetic origin.

- exposure to a known human teratogen is already included in the list of potential confounders (within maternal exposure and lifestyle habits in Section 8.3.3). However, in the case where there are insufficient number of events to consider regression adjustment, a sensitivity analysis will be performed excluding participants with exposure to known teratogens to address this potential confounder.

- a sensitivity analysis will be performed stratified on any abnormal finding (yes/no) among those with prenatal testing prior to enrollment.

- exposure in the 2nd and 3rd trimesters will be considered for those selected major birth defects that are potentially biologically plausibly related to later pregnancy exposure, e.g., craniosynostosis" [Jones, 2013]

### 8.7.3. General considerations for data analyses

A detailed SAP will be prepared and finalized prior to the conduct of any study analysis or reporting.

Analyses of data at the completion of the study will be performed according to the methods as described in Section 8.7.1 and Section 8.7.2.

Since each outcome and each comparison has its unique potential confounder list and set of subjects, propensity scores are generated for each analysis endpoint separately.

**Also, a description of specific major structural birth defects will be provided in listings.**

## 8.8. Quality control and quality assurance

As noted in Section 8.7, quality control measures are in place throughout the entire period of data collection and data entry. Training and retraining of study staff is monitored per study SOP, and validation of data entry for critical study variables is conducted for 100% of study participant interactions. Data exported for interim and final analyses for this study will be checked for logical errors, and range checks are performed. All major birth defect classifications will be verified by the study investigators.

Data will be reviewed on an interim basis by the external advisory board. This board consists of representation from the U.S. Centers for Disease Control and Prevention Center for Birth Defects and Developmental Disabilities, a maternal-fetal medicine and reproductive toxicologist, a geneticist, and disease-specific specialty representative. This standing committee meets annually and reviews all interim and final study reports as well as manuscripts that are produced from the study results. The committee comments on the study progress and poses questions that arise which are addressed by the investigators.

Final data sets are cleaned and utilized for preparation of the analyses and study reports. All analyses (coding and output) are reviewed by the lead study statistician and at least

one other staff statistician. Study reports are reviewed by the Study Manager and the Investigators. All data sets and analytic files are archived indefinitely at the OTIS Research Center, and analyses can be replicated as necessary.

## 8.9. Limitations of the research methods

Potential limitations of the research methods are as follows:

The study relies on a volunteer sample, which may or may not be entirely representative of all women who take belimumab during pregnancy. However, for a product used for a relatively rare condition, this is likely to be one of the only methods of obtaining safety information for pregnancy exposures because of the ability to target key patient and provider groups, particularly physicians who treat patients with SLE, to increase awareness about the study. Due to the nature of self-reported interviews at different times within and post pregnancy there may be differential recall depending on timing of interviews. However, this is addressed by monitoring for comparability in cohorts in gestational timing of enrollment, standardizing windows for completing interviews, and validation with, medical records.

Although all possible measures will be taken to ensure registry awareness and outreach including marketing via websites, social media, print media, scientific conferences, etc., it is known that enrollment rates, particularly in previous belimumab registry, have been poor (BEL114256). Pregnancy registry enrollment rates are subject to drug utilization among pregnant women. Drugs with relatively low use among pregnant women (≤20/100,000 live birth pregnancies) had less successful enrollment in pregnancy registries [Bird, 2018]. In this study, we have proposed a sample size that accounts for operational feasibility, thereby ensuring generation of data that will provide insights into effects of belimumab on pregnancy outcomes to the patients and prescribers in a timely manner.

The sample size that is achievable for a product used for a relatively rare condition limits the power to detect differences, especially for rare outcomes such as major birth defects. The study will also be limited in ability to address increased risks for spontaneous abortion as the highest risk for spontaneous abortion occurs in the gestational weeks prior

to when women would typically enroll in the study. However, based on expected gestational timing of enrollment, spontaneous abortion rates in late first trimester and early second trimester will be analyzable. Further, measurement of a rare outcome may also limit the ability to adjust for potential confounders in multivariable analyses. Where possible due to sufficient events, a propensity score is planned to include relevant confounders.

A bias of this study might be associated with right truncation or censoring. This occurs when pregnancies end the follow-up before the outcome is known (censoring), or with unknown outcomes (truncation). Since pathology is rarely available for spontaneous abortions and terminations for social reasons, most cohorts consider the prevalence of malformations in livebirths rather than the cumulative incidence over gestation. Failure to include defects detected among terminations can underestimate the incidence of malformations and decrease power but, if the missingness is random with respect to exposure, the relative risk for malformations will be unbiased. Additionally, for other outcomes that are also dependent on timing of enrollment in relation to the outcome occurrence (e.g. elective termination and ectopic/molar pregnancy) there may be incomplete data. The dysmorphology exam for minor birth defects may not be performed consistently across all infants and thus there may be missing data for some infants. Medical records may also not be available for all women or infants and there could be missing data from these sources as well. Efforts will be made to enroll a disease comparison group that is of similar disease severity however, there could be differences between the cohorts that may not be able to be adjusted or accounted for due to the nature and collection of the data.

Strengths of the study design are the ability to build on the referral network of OTIS member services across the U.S. and Canada to identify belimumab-exposed pregnancies as well as appropriate comparison group pregnancies, the OTIS research groups' track record of excellent subject retention (<5% lost to follow-up) [Chambers, 2010; Chambers, 2016; Chambers, 2019b]. In addition, the study design allows for appropriate comparison to a treated disease group, and for appropriate attention to confounding or effect modification.

### 8.9.1. Study closure/uninterpretability of results

In consultation with the Scientific Advisory Board, discontinuation of the study will be considered at such time as:

- sufficient information has accumulated to meet the scientific objectives of the study
- other methods of gathering appropriate information become achievable or are deemed preferable
- the feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or losses to follow up. Upon initiation of recruitment, the study is expected to continue to recruit for five years with recruitment approximating 40 patients exposed to belimumab per year. Regular review of enrollment numbers will be performed, and numbers compared to the sponsor's data and other external data on the use of belimumab to determine if use among women of reproductive age is consistent with enrollment rates in the cohort study. Enrollment will also be reviewed with respect to key awareness activities.
- If the Sponsor discontinues manufacturing belimumab they may withdraw from the study upon written notification.

## 8.10. Other aspects

None

# 9. PROTECTION OF HUMAN SUBJECTS

## 9.1. Ethical approval and subject consent

The study is approved through the University of California San Diego Human Research Protections Program (Institutional Review Board or IRB). All study participants must agree to the IRB-approved oral consent form at the time of enrollment and before completing the intake interview. Each participant must subsequently sign the IRB-approved informed consent document in order to continue to participate in the Registry. Each participant is also asked to sign for release of medical information to allow the Registry to obtain information on the pregnancy and the pregnancy outcome from the participant's obstetrician, the hospital of delivery, and any other health care specialist, and for the infant from the infant's pediatrician.

The original oral and signed informed consent documents, and copies of the medical records release forms will be maintained at the Research Center.

Pregnant women under the age of 18 who are eligible for the study and who wish to participate will require written consent of their parent or guardian prior to the initial intake interview and written assent from themselves. Consent/assent forms and study participation materials are available in English or Spanish. Impact of non-French materials will be monitored and assessed.

## 9.2. Subject confidentiality

The Registry makes every effort to assure participant confidentiality within the Registry. Personally identifiable information is maintained in secure files with restricted access limited to only authorized personnel.

Registry Investigators, data collection and management staff reside at the MotherToBaby/OTIS Pregnancy Studies Research Center located at the University of California, San Diego. These personnel, under the supervision of the Investigators, have access to the physical files and electronic data, have documented completion of human subjects research training, and are listed individually as authorized to have access to the study data on the study IRB-approved research plan.

Sponsor representatives through the Registry Scientific Advisory Committee have access to de-identified summary data as part of the periodic annual review and the final study report. Final study data files for analysis are stripped of identifiers and archived without personal identifiers.

Care will be taken to ensure that no individual participant is identifiable in the data tables published in the Annual Reports, or other presentations or publications.

# 10. LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA

The authors confirm that study data is Individual Human Data (IHD) owned by GSK and OTIS and that:

- The proposed use of the IHD is **Study Use*** as outlined in the patient consent.

*Study Use means - the use of IHD is as stated in the original study protocol and/or aligned with the informed consent form to answer the study objectives and satisfy regulatory requirements and learn more about the product studied and the disease/condition studied. This includes bringing the product to market or maintaining market access which includes working with government agencies, insurers or health care payers and aiding GSK's understanding of clinical efficacy, safety, or effectiveness of the product.

# 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

A Safety Management Plan (SMP) will be developed for the study and will provide detailed information on the study specific pharmacovigilance processes and procedures. The SMP will include the following elements to ensure a comprehensive approach to safety event collection and reporting:

- OTIS Pharmacovigilance training
- Safety-specific roles
- AEs, medical devices, pregnancy exposures, and incidents collection and reporting processes
- AE, medical devices, pregnancy exposure, and incident collection forms
- Frequency of data review
- Reporting process and timelines
- Reconciliation process
- SMP monitoring process
- Provision of interim and final study reports

This study adopts the following ICH definitions:

Adverse event: *Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.*

- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product including those used in combination with a medical device. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event), and adverse events associated with circumstances of Overdose whether accidental or intentional, Medication Errors, Abuse or effects of drug withdrawal, or Misuse or those related to a deficiency occurring with a medical device.

Serious adverse event: *any untoward medical occurrence that at any dose that 1) results in death, 2) is life threatening, 3) requires inpatient hospitalization or prolongs existing hospitalization, 4) results in persistent or significant disability/incapacity or 5) is a congenital anomaly.*

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

The purpose of the Belimumab Pregnancy Exposure Study is to monitor planned and unplanned pregnancies exposed to belimumab and to evaluate the possible teratogenic effect of this medication. For belimumab exposed pregnancies pre-defined specific pregnancy outcomes that are classified as serious adverse events (SAEs) will be identified and reported. These selected SAEs include Major Birth Defects (MBD),

SAB (including ectopic and molar pregnancies), stillbirth and neonatal death and serious infant infections. These events will be reported to the sponsor's safety department within 24 hours. In addition, if the OTIS Research Centre investigators become aware of an event following belimumab exposure that meets the definition of serious adverse event as stated above, these will be reported to the sponsor's safety department within 24 hours. SAEs which occur in both mothers and infants through follow-up will be reported.
If during the study, the OTIS Research Centre investigators become aware of an adverse event explicitly attributed to any known GSK product, this will also be reported to the sponsor's safety department within 24 hours.

The interim and final study reports will include the SAEs that are the study endpoints as part of the hypotheses being tested, and a summary of SAEs and AEs.

# 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

## 12.1. Target audience

Healthcare providers treating women with SLE (rheumatologists, nephrologists, maternal-fetal medicine specialists, and internists) and regulatory authorities.

## 12.2. Study reporting and publications

Key design elements of this study will be posted in publicly accessible databases such as Clinical.trials.gov. Furthermore, key results of this study will be posted in publicly accessible databases within the required timeframe from completion of the data collection where applicable.

Interim reports will be prepared on study progress annually by study investigators and reviewed by GSK. Additionally, the standing Scientific Advisory Board meets annually and reviews all interim data, and interim reports. Interim reports will include descriptive analyses with study tables (.g. recruitment, enrollment, demographic and baseline

characteristics, primary, secondary pregnancy and infant outcomes, line listings and preliminary conclusions of the Advisory Board on the safety of Benlysta in pregnancy.

Upon closure of the study, a final report will be generated by the study investigators, reviewed by the standing advisory committee and GSK and then submitted by GSK to the relevant regulatory authorities.

The data may also be considered for reporting at scientific conferences or for publication in scientific journals. Preparation of such manuscripts will be prepared independently by study investigators and in accordance with the current guidelines for Strengthening the Reporting of Observational studies in Epidemiology [von Elm, 2008]. Study investigators will follow the international committee of medical journal editors (ICMJE) recommendations for authorship and acknowledgements. GlaxoSmithKline will be entitled to view the results and interpretations included in the manuscript prior to submission for publication.

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# 14. GLOSSARY

| Term | Study Definition |
|---|---|
| Developmental concerns | Defined as an abnormal score within the scoring guidelines of the Ages and Stages Questionnaire (ASQ) [Squires, 2009]. The ASQ is administered at 12 months of age as a screening tool for developmental milestones by parent report. The ASQ-3 will be sent electronically to the participant or, if the participant prefers, a hard copy questionnaire will be mailed for completion. |
| Eclampsia | A life-threatening condition that is considered a complication of severe pre-eclampsia and characterized by coma and/or seizures that are unrelated to a preexisting brain condition. |
| Ectopic pregnancy | Implantation of the conceptus outside of the uterus. |
| Elective termination | Defined as deliberate termination of pregnancy at any time in gestation by surgical or medical means. Reasons for elective abortions are captured and are classified as due to medical reasons or social reasons. |
| Gestational diabetes | Glucose intolerance with onset during pregnancy and expected to resolve after delivery. |
| Gestational hypertension | The development of high blood pressure with onset during pregnancy (usually after 20 weeks gestation); this condition is not associated with proteinuria or other signs of pre-eclampsia and may also be known as pregnancy-induced hypertension. |
| Last menstrual period (LMP) | The first day of the last menstrual period prior to conception. |
| Major birth defect | Defined and classified using the CDC coding manual [CDC, 2017], which may be reported by the participant or by medical record. The CDC coding manual is utilized to classify defects reported through the ongoing population-based Metropolitan Atlanta Congenital Defects Program (MACDP) and is based on agreed-upon criteria by CDC investigators for major birth defects regardless of etiology. Malformations are reviewed by the study dysmorphologists. |
| Maternal death | The death of a woman while pregnant or within 1 year of pregnancy regardless of cause |

| Term | Study Definition |
|---|---|
| Metropolitan Atlanta Congenital Defects Program (MACDP) | A program that monitors all major birth defects in 5 counties of the metropolitan Atlanta area [Clayton, Cobb, DeKalb, Fulton and Gwinnett] with approximately 50,000 annual births from a population of about 2.9 million. MACDP acts as the model for many state-based programs and as a resource for the development of uniform methods and approaches to birth defect surveillance. |
| Minor birth defect pattern | A minor birth defect is defined as a defect that has neither cosmetic nor functional significance to the child and as itemized on the study-related dysmorphology examination form [Jones, 2013]. Minor defect pattern will be defined using the following two steps: 1) identify infants with at least 3 minor structural defects of any type in the belimumab-exposed group and 2) from among infants with at least 3 minor structural defects in the belimumab-exposed group, identify any 2 or more unrelated infants with the same 3 specific minor structural defects. The prevalence of each specific pattern or patterns, if any, that are identified in the belimumab-exposed infants will be identified in the unexposed SLE comparator group. As an example, if 2 infants in Cohort 1 had the following minor structural defects: "hair pattern unruly", “prominent nasal bridge", and "clinodactyly 5th finger bilateral", this would constitute one specific pattern of minor structural defects. For each specific pattern identified in Cohort 1, infants in Cohorts 2 who have the same specific pattern(s) are selected to comprise the numerator for those cohorts. In infants who have more than one specific patterns of at least 3 minor structural defects, each specific pattern will qualify as its own endpoint; therefore, the infant would be counted more than once. |
| Molar pregnancy | Molar pregnancy is also known as hydatidiform mole. It is a rare complication of pregnancy characterized by the abnormal growth of trophoblasts, that results in a gestational trophoblastic tumor.<br><br>There are two types of molar pregnancy, complete molar pregnancy and partial molar pregnancy. In a complete molar pregnancy, the placental tissue is abnormal and swollen and appears to form fluid-filled cysts. There's also no formation of fetal tissue. In a partial molar pregnancy, there may be normal placental tissue along with abnormally forming |

| Term | Study Definition |
|---|---|
| | placental tissue. There may also be formation of a fetus, but the fetus is not able to survive, and is usually miscarried early in the pregnancy |
| Postnatal growth deficiency | Defined as postnatal size at approximately 1 year of age (for the study) (weight, length or head circumference) less than or equal to the 10th percentile for sex and age using National Center for Health Statistics (NCHS) pediatric growth curves, and adjusted postnatal age for premature infants if the postnatal measurement is obtained at less than 1 year of age. [CDC, 2000]. |
| Pre-eclampsia | Pre-eclampsia or preeclampsia is defined as hypertension in conjunction with at least one of the following: proteinuria; thrombocytopenia; impaired liver function; renal insufficiency; pulmonary edema; or visual or cerebral disturbances. The disorder usually occurs after 20 weeks of pregnancy and worsens over time. |
| Preterm delivery | Defined as a spontaneous or induced delivery at <37 gestational weeks, reported by the mother and validated through the medical record when available. Please refer to Section 8.3.1 for further description of the method for defining gestational age and therefore preterm birth. |
| Prolonged labor | Labor lasting for approximately 20 hours or more |
| Small for Gestational Age (SGA) | Defined as live born infants who are ≤10th centile on birth weight for infant sex and gestational age will be considered small for gestational age. The U.S. Centers for Disease Control and Prevention (NCHS) [CDC, 2000] growth charts will be used for full term infants, and the Olsen growth charts will be used for preterm infants [Olsen, 2010]. The outcome of birthweight is reported by the mother and validated through the medical record when available. |
| Spontaneous abortion (SAB) | Defined as spontaneous pregnancy loss prior to 20 weeks' gestation (including ectopic/molar pregnancy). In this study, since women enroll after recognition of pregnancy, SABs are only identified after enrollment in clinically recognized pregnancies. This outcome is reported by the mother and validated through the medical record, where available. |
| Stillbirth | Defined as a fetal death that occurs ≥20 weeks' gestation. |

| Term | Study Definition |
|---|---|
| Serious infections up to 1 year of age | Defined infections requiring hospitalization identified in live born infants up to one year of age |
| Thrombocytopenia | A decreased number of platelets in the blood associated with an increased risk of bleeding. A peripheral blood platelet count less than 150,000/ L. |
| Thrombosis | Formation of a blood clot, known as a thrombus, within a blood vessel |

# 15. ANNEXURES

Core table shells and figures will be included in the Statistical Analysis Plan

## 15.1. ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

**SLE Disease Severity Assessmen**t: Patient disease severity assessment that exists presently in clinical practice includes: Patient Global Assessment (ptGA), Lupus Impact Tracker (LIT) as well as others (Mikdashi, 2015). Physician disease severity assessment used in clinical practice includes: International Collaborating Clinics-SLICC/American College of Rheumatology-ACR damage index score (SDI), Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI), as well as others. Disease severity assessment tools used for the study will be further described in the Statistical Analysis Plan.

## 15.2. ANNEX 2. LIST OF KNOWN HUMAN TERATOGENS

| Exposure | Notes | References |
|---|---|---|
| ACE inhibitors | | https://mothertobaby.org/fact-sheets/ace-inhibitors-pregnancy/ |
| Acitretin | | https://mothertobaby.org/fact-sheets/tretinoin-retin-a-pregnancy/ |
| Alcohol, Heavy | **>14 drinks per week for ≥4 weeks**. | https://mothertobaby.org/fact-sheets/alcohol-pregnancy/ |
| Aminopterin | | Briggs GG, Freeman RK, Yaffe SJ. 2011. Aminopterin. In: Drugs in pregnancy and lactation. 9th ed. Lippincott Williams and Wilkins. 2011 pp. 54–55 Fetal aminopterin syndrome. Bissonnette B, & Luginbuehl I, & Marciniak B, & Dalens B.J.(Eds.), (2006). Syndromes: Rapid Recognition and Perioperative Implications. McGraw Hill. https://accessanesthesiology.mhmedical.com/content.aspx?bookid=852&sectionid=49517572 |
| Antiseizure / Anticonvulsant Medications1 | | https://mothertobaby.org/fact-sheets/lamotrigine/ https://mothertobaby.org/fact-sheets/carbamazepine-pregnancy/ https://mothertobaby.org/fact-sheets/valproic-acid-pregnancy/ https://mothertobaby.org/fact-sheets/oxcarbazepine/ https://mothertobaby.org/fact-sheets/topiramate/ |
| Antineoplastics, Other | | https://www.cdc.gov/niosh/topics/repro/antineoplastic.html |
| Cocaine | | https://mothertobaby.org/fact-sheets/cocaine-pregnancy/ |
| Cytomegalovirus (CMV) | | https://mothertobaby.org/fact-sheets/cytomegalovirus-cmv-pregnancy/ |
| Type I and Type II Diabetes | | https://mothertobaby.org/fact-sheets/type-1-and-type-2-diabetes/ |
| Etretinate | | https://embryo.asu.edu/pages/retinoids-teratogens Happle R, Traupe H, Bounameaux Y, Fisch T. Teratogene Wirkung von Etretinat beim Menschen [Teratogenic effects of etretinate in humans]. Dtsch Med Wochenschr. 1984 Sep 28;109(39):1476-80. German. |
| Fever, High | **102 degrees or higher for 24 hours or longer** | Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Maternal fever and birth outcome: a prospective study. Teratology. 1998 Dec;58(6):251-7. https://mothertobaby.org/fact-sheets/hyperthermia-pregnancy/ |

| | | |
|---|---|---|
| Fluconazole | **≥7 days total** (consecutive or non-consecutive) and/or 400-800 mg/day dose | https://mothertobaby.org/fact-sheets/fluconazole-pregnancy/ ;<br>Howley MM, Carter TC, Browne ML, Romitti PA, Cunniff CM, Druschel CM; National Birth Defects Prevention Study. Fluconazole use and birth defects in the National Birth Defects Prevention Study. Am J Obstet Gynecol. 2016 May;214(5):657.e1-9.<br>https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communicationuse-long-term-high-dose-diflucan-fluconazole-during-pregnancy-may-be |
| Isotretinoin | | https://mothertobaby.org/fact-sheets/isotretinoin-accutane-pregnancy/ |
| Lenalidomide (analog of thalidomide) | | Bwire R, Freeman J, Houn F. Managing the teratogenic risk of thalidomide and lenalidomide: an industry perspective. Expert Opin Drug Saf. 2011 Jan;10(1):3-8. doi: 10.1517/14740338.2011.527331. Epub 2010 Dec 2. PMID: 21121869.<br>https://mothertobaby.org/fact-sheets/thalidomide-pregnancy/ |
| Lithium | | https://mothertobaby.org/fact-sheets/lithium-pregnancy/ |
| Methimazole | | https://mothertobaby.org/fact-sheets/propylthiouracil-ptu/<br>Hackmon R, Blichowski M, Koren G. The safety of methimazole and propylthiouracil in pregnancy: a systematic review. J Obstet Gynaecol Can. 2012 Nov;34(11):1077-1086.. |
| Methotrexate | | https://mothertobaby.org/fact-sheets/methotrexate-pregnancy/ |
| Propylthiouracil (PTU) | | https://mothertobaby.org/fact-sheets/propylthiouracil-ptu/<br>Hackmon R, Blichowski M, Koren G. The safety of methimazole and propylthiouracil in pregnancy: a systematic review. J Obstet Gynaecol Can. 2012 Nov;34(11):1077-1086.. |
| Radiation, High Dose | ≥5 rads to the uterus | https://mothertobaby.org/fact-sheets/ionizing-radiation-workplace-pregnancy/ |
| Rubella | | https://mothertobaby.org/fact-sheets/measles-mumps-rubella-mmr-vaccine-pregnancy/ |
| Thalidomide | | https://mothertobaby.org/fact-sheets/thalidomide-pregnancy/ |
| Toxoplasmosis | | https://mothertobaby.org/fact-sheets/toxoplasmosis-pregnancy/ |
| Varicella | Primary case of chicken pox | https://mothertobaby.org/fact-sheets/varicella/ |

| | | |
|---|---|---|
| Warfarin (coumadin, Jantoven) derivatives | | Dhillon SK, Edwards J, Wilkie J, Bungard TJ. High-Versus Low-Dose Warfarin-Related Teratogenicity: A Case Report and Systematic Review. J Obstet Gynaecol Can. 2018 Oct;40(10):1348-1357.<br>Hall JGPauli RMWilson KM Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med. 1980;68122- 140<br>Ginsberg JSHirsh JTurner CD et al. Risks to the fetus of anticoagulation therapy during pregnancy. Thromb Haemost. 1989;61197- 203 |
| Zika, Confirmed | Positive test result | https://mothertobaby.org/fact-sheets/zika-virus-pregnancy/ |

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| Reason for signing: Approved | Name: Keele Wurst<br>Role: Approver<br>Date of signature: 29-Mar-2022 12:28:54 GMT+0000 |

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