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PASS Protocol

The Benralizumab Pregnancy Exposure Study: A VAMPSS Post-Marketing Surveillance Study

Sponsor: AstraZeneca

Principal Investigator: Christina Chambers, PhD, MPH

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	AstraZeneca AB SE-151 85 Sodertalje SWEDEN
MAH contact person	[redacted] AstraZeneca AB Pepparedsleden 1, 431 83 Mölndal Sweden [redacted]

Approved by: [redacted]

5 SEPT, 2018
Date

EU Qualified Person Responsible for Pharmacovigilance

PASS INFORMATION

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Research question and objectives	The objectives of the Pregnancy Exposure Study are to monitor planned and unplanned pregnancies exposed to benralizumab and to evaluate the possible teratogenic effect of this medication relative to the primary pregnancy outcome of major structural birth defects and the secondary pregnancy outcomes of preterm delivery, small for gestational age infants, spontaneous abortion, stillbirth, elective termination and small for age postnatal growth to one year of age.
Country (-ies) of study	United States and Canada (North America)
Author(s)	Christina Chambers, PhD, MPH Professor of Pediatrics School of Medicine University of California San Diego 9500 Gilman Drive, MC 0828 La Jolla, CA 92093 Tel: [redacted] Email: [redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AAAAI	American Academy of Allergy, Asthma and Immunology
AZ	AstraZeneca
CDC	Centers for Disease Control and Prevention
EMA	European Medicines Agency's
FDA	Food and Drug Administration
FPI	First Patient In
GA	Gestational Age
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing Authorization Holder
MCM	Major Congenital Malformation
NCHS	National Center for Health Statistics
OTIS	Organization of Teratology Information Services
PASS	Post-Authorization Safety Studies
PRAC	Pharmacovigilance Risk Assessment Committee
PTB	Preterm Birth
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedures
UCSD	University of California, San Diego
US	United States
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System

3. RESPONSIBLE PARTIES

Sponsor: The Marketing Authorisation Holder (MAH) will serve as the collaborator of this study. It is the responsibility of the MAH to ensure review of the study plan, progress reports and final reports, and compliance of study materials, reports and protocols to the Post Approval Safety Studies (PASS) guidance of the European Medicines Agency and other regulatory authorities. It is the responsibility of the Study Coordinating site to abide by all internationally accepted standards for ethical study conduct, monitoring and reporting.

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 Center is the cohort arm of the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) in collaboration with the American Academy of Allergy, Asthma and Immunology (AAAAI).

The OTIS Research Center will conduct the study with review and input from the MAH. The OTIS Research Center will receive referrals from the North American OTIS network of teratogen information counselling services. The North American OTIS network is a network of university and health department based 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 healthcare providers.

The American Academy of Allergy, Asthma and Immunology (AAAAI) will assist the OTIS Research Center in raising awareness of the study among healthcare providers who treat women with more severe asthma and will be responsible for organizing and hosting the annual Scientific Advisory Committee meetings for this study.

Principal Investigator:
Christina Chambers, PhD, MPH
University of California, San Diego
9500 Gilman Dr. #0828
La Jolla, CA, CA 92093-0828
Phone: [redacted]
Email: [redacted]

4. ABSTRACT

Title: The Benralizumab Pregnancy Exposure Study: A VAMPSS Post-Marketing Surveillance Study

Rationale and background: Asthma in women of child bearing age and pregnant women is common. Although the majority of patients with asthma can be effectively treated with available controller medications, a subset of patients does not adequately respond to current standard therapy. Benralizumab (Fasenra™) is an eosinophil depleting monoclonal antibody (IgG1 kappa) indicated in EU as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β -agonists.

Pregnancy exposure data for benralizumab is insufficient to inform regarding drug-associated risks to the fetus or mother. Nonetheless, benralizumab is likely to be utilized by pregnant women when they and their doctors believe that risk/benefit considerations favor its use. Also, given the frequency of unplanned pregnancies, and the long half-life of the drug, inadvertent exposure in pregnancy is likely, even if treatment is discontinued as soon as pregnancy is suspected or confirmed. We therefore propose a pregnancy exposure cohort study to assess the safety of benralizumab use during pregnancy. Information regarding the safety of benralizumab in human pregnancy is essential from a public health perspective to help inform clinical practice.

The Study fulfils a category 3 post-authorisation measure to the The European Medicines Agency's (**EMA**) Pharmacovigilance Risk Assessment Committee (**PRAC**).

Research question and objectives: The objectives of the Benralizumab Pregnancy Exposure Study are to monitor planned and unplanned pregnancies exposed to benralizumab and to evaluate the potential teratogenic effect of this medication relative to the primary pregnancy outcome of major structural birth defects and the secondary pregnancy outcomes of preterm delivery, small for gestational age infants, spontaneous abortion, stillbirth, elective termination and postnatal growth to one year of age.

Study design: This is a prospective, observational, exposure cohort study of pregnancy and infant outcomes in women with asthma exposed to benralizumab anytime during pregnancy, or within 8 weeks prior to the first day of the last menstrual period (LMP). The birth prevalence or incidence of outcomes in women exposed to benralizumab, and their infants, will be compared to those observed in two unexposed comparator groups: a disease-matched comparison group of women who have not used benralizumab during pregnancy or within 8 weeks of their last menstrual period (LMP), but who have used other anti-asthmatic medications (treated disease comparison group), and a comparison group of healthy women

who do not have a diagnosis of asthma, have not had exposure to a known human teratogen, and have not taken benralizumab in pregnancy (healthy comparison group).

Population: The study population includes pregnant women who reside in the US or Canada who have or have not used benralizumab anytime in pregnancy for asthma.

Three groups of participants will be enrolled and followed for pregnancy and infant outcomes:

- Pregnant women with asthma exposed to benralizumab anytime during pregnancy or within 8 weeks prior to LMP
- Pregnant women currently treated for asthma not exposed to benralizumab during pregnancy or within 8 weeks prior to LMP
- Pregnant women who are not diagnosed with asthma, have not had exposure to a known human teratogen, and have not taken benralizumab in pregnancy

Variables: Outcome variables include major structural birth defects, spontaneous abortion, stillbirth, elective termination, preterm delivery, infant birth size, postnatal growth of live born children 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 maternal age, race/ethnicity, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, medication, vaccine and vitamin/mineral exposures, prenatal tests, and measures of disease severity. Exposure will be defined as benralizumab treatment by maternal report and verified by medical record review, with detailed information on the gestational timing, route of administration, dose, and dates of exposure. Details regarding definitions will be provided in the Statistical Analysis Plan (SAP) to be developed separately and submitted to the agency prior to the submission of the first interim report.

Data sources: Data will be collected using maternal interview(s), medical records (obstetric, delivery hospital, pediatric, allergist and/or other specialty provider), and pregnancy exposure diary. Maternal interview data will be recorded on hard copy forms, and medical record abstraction data will be recorded on electronic forms, and these records will be retained by OTIS. Maternal interview 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 the OTIS studies.

Study size: The target sample size for the study is 200 women in the benralizumab-exposed cohort; 300 women in the treated diseased cohort; and 300 women in the non-diseased cohort.

Statistical method: Demographic and baseline characteristics will be compared between the cohorts. The primary analysis will be a comparison of the prevalence rate of major structural defects in live born infants between the benralizumab-exposed cohort and the treated disease cohort. Where numbers permit, multivariable analyses will be conducted to determine the

relationship of benralizumab with the primary outcome of major structural birth defects, and separately for each of the secondary outcomes of small for gestational age, preterm delivery, spontaneous abortion, stillbirth, elective termination and small for age postnatal growth. There will be no formal hypothesis testing, rather point estimates of the rate ratios along with confidence intervals will be presented.

Milestones: The study is planned for 7 years from start of enrollment (first patient in (FPI) to study completion). There will be 5 years of active recruitment, with an interim report reviewed by the Scientific Advisory Committee each year. The final report with statistical analysis according to the SAP will be prepared at the end of the study.

5. AMENDMENTS AND UPDATES

Table 1 Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
Protocol Version 2.0	*03 September 2018*	*Milestones*	Clarify timelines	Response to comments from the EMA
		Sections 4 & 9.5 & 9.7	Revise the sample size justification to reflect the focus is to characterize the degree of uncertainty around estimates, rather than to be used for any formal statistical hypothesis testing, and add 80% CIs to the statistical analyses section. Clarify the focus for analysis of clinical relevance through signal detection, rather than analysing statistical significance	Response to comments from the EMA
		Sections 4, 9.6.1, 9.7.1, 10.1.4, 12.1.2	interim report; annual interim report; interim annual report referenced throughout the protocol are all now referred to as “interim report”	Consistency
		Section 11	Added method of causality assessment of adverse events	Response to comments from the EMA

6. MILESTONES

Table 2 Study milestones

Milestone	Planned date
Start of data collection	September 2018
End of data collection	August 2025
Registration in the EU PAS register	Study not registered
Final report of study results	September 2026

7. RATIONALE AND BACKGROUND

Asthma is a common, life-long inflammatory disease of the airways that affects children and adults of all ages. It is one of the most common long-term diseases worldwide, and can be life threatening. The prevalence of asthma in adults in the United States is estimated at 7% (National Health Interview Survey, 2001-2003). Prevalence is higher in females than males and has considerably increased in recent years (National Health Interview Survey, 2001-2003). Symptoms come and go and include shortness of breath, wheezing, chest tightness and cough. The cause of asthma is unknown; however, a family history of asthma, eczema or allergy makes it more likely that an individual will develop asthma.

Although the majority of patients with asthma can be effectively treated with available controller medications, a subset of patients do not adequately respond to current standard therapy. This subset of severe asthma is a heterogenous disease that affects approximately 5-10% of asthmatic patients but is responsible for a disproportionate percentage of the health care costs associated with asthma (Antonicelli et al., 2004; Godard, 2002; Moore et al., 2007). About thirty percent of severe asthma patients are reported to have severe eosinophilic asthma in which their symptoms are associated with too many eosinophils ($\geq$300 cells/mm^3) (a type of white blood cells) in the blood and in phlegm in the airways (R.S.Zeiger, 2018)).

Benralizumab is an eosinophil depleting monoclonal antibody (IgG1 kappa). In Europe, it is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists. Benralizumab is indicated for add-on maintenance treatment of patients with severe asthma, aged 12 years and older in the U.S. and adult patients in Canada, and with an eosinophilic phenotype. It is administered as a 30 mg subcutaneous injection given every 4 weeks for the first 3 doses, followed by 30 mg subcutaneous injection every 8 weeks thereafter. Recently, clinical efficacy of benralizumab 30 mg SC in asthma was confirmed in Phase 3 global safety and efficacy trials in patients on high dose ICS/LABA (Bleecker et al., 2016; FitzGerald et al., 2016; Nair et al., 2017).

The prevalence of asthma and severe asthma in women of child bearing age, coupled with the chronic nature of treatment and the schedule of doses with which benralizumab is given, makes inadvertent exposure in pregnancy likely. The fact that it is given by injection makes the ascertainment of exposed pregnancies early in gestation and documentation of gestational timing of exposure more feasible than in circumstances where a drug is taken only as needed and not administered by a health care provider. We therefore propose a pregnancy exposure cohort study to assess the safety of benralizumab in pregnancy.

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

8. RESEARCH QUESTION AND OBJECTIVES

The purpose of the Benralizumab Pregnancy Exposure Study is to evaluate the effect of benralizumab exposure on pregnancy and infant outcomes compared to unexposed diseased and healthy unexposed pregnancies. Below are the study primary and secondary outcomes:

Primary outcome:

- Major structural birth defects

Secondary outcomes:

- Spontaneous abortion/miscarriage
- Stillbirth
- Elective termination/abortion
- Preterm delivery
- Small for gestational age infants
- Small for age postnatal growth of live born children to 1 year of age

9. RESEARCH METHODS

9.1 Study design

This is a prospective, observational, exposure cohort study of pregnancy outcomes in women with asthma exposed to benralizumab anytime during pregnancy or within 8 weeks prior to Last Menstrual Period (LMP) compared to pregnancy outcomes in women with a diagnosis of asthma who are currently treated for asthma but who have not used benralizumab during pregnancy or within 8 weeks prior to LMP but have used other anti-asthmatic medications, (treated disease comparison group), and pregnancy outcomes in women not diagnosed with asthma who have not been exposed to any known teratogens but have potentially been exposed to non-teratogenic agents (non-diseased comparison group).

The study is conducted by the 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 network of teratogen information services as well as other sources of recruitment (see Section 9.2.1 for modalities of recruitment).

The study design is appropriate for the study objectives in that mothers are enrolled 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 benralizumab exposure in pregnancy, and two appropriate comparison groups. Data obtained for the treated diseased group assists with evaluation of the contribution of the underlying maternal disease to adverse pregnancy outcomes, and provides an appropriate comparison group for the benralizumab-exposed cohort. This is essential, in that maternal asthma itself has been associated with a wide variety of adverse pregnancy outcomes (Murphy et al., 2011; J. A. Namazy et al., 2013; Rejno et al., 2014). The non-asthmatic comparison group allows for comparison of asthmatic to non-asthmatic women. If the distribution of underlying disease severity is similar in both the benralizumab and the treated disease group, this could further illuminate the potential contribution of the disease (and disease-severity) to outcomes.

Women who agree to enroll will be consented orally over the telephone, and will then complete the initial telephone interview (See Section 10.1.3 for the consent process). Depending on the gestational timing of enrollment, a number of subsequent telephone interviews will be conducted during pregnancy and after birth. After women sign for release of medical records, medical records for both the woman and infant will be obtained and abstracted for information to validate exposures and outcomes. Enrolled women will be followed until the completion of pregnancy and infants followed up to one year after birth to determine the outcome of pregnancy with respect to primary and secondary study outcomes (refer to Table 7, Section 9.6.2 for more information on the timing of study events)

9.2 Setting

The study population consists of three cohorts of pregnant women (See Section 9.5 for sample size).

Participants will be recruited into the three cohorts concurrently, on the basis of the following inclusion/exclusion criteria:

Cohort 1: Benralizumab-Exposed

Inclusion Criteria:

- Currently pregnant women diagnosed with asthma who contact the OTIS Research Center and who have been exposed to benralizumab for any number of days, at any dose, and at

any time from 8 weeks before the first day of LMP up to and including the end of pregnancy.

- Eligible participants will be currently pregnant women who agree to the conditions and requirements of the study including the interview schedule and release of medical records.

Exclusion Criteria:

- Women who have had exposure to another biologic, used for any indication, anytime during pregnancy or within 8 weeks of LMP.
- Women will not be eligible for Cohort 1 if they first contact the OTIS Research Center after prenatal diagnosis of a major structural birth defect.
- Restrospective cases (outcome of pregnancy known prior to enrollment).
- Women who have enrolled in the current study with a previous pregnancy.

Cohort 2: Treated Diseased Comparison

Inclusion Criteria:

- Currently pregnant women diagnosed with asthma and exposed to asthma medications for any number of days, at any dose, and at any time from LMP up to the date of enrollment, who contact the OTIS Research Center but who were not exposed to benralizumab during pregnancy or within 8 weeks prior to LMP.
- Eligible participants will be currently pregnant women who agree to the conditions and requirements of the study including the interview schedule and release of medical records.

Exclusion Criteria:

- Women with exposure to benralizumab any time during pregnancy or within 8 weeks prior to LMP.
- Women will not be eligible for Cohort 2 if they first come in contact with the OTIS Research Center after prenatal diagnosis of a major structural birth defect.
- Retrospective cases (outcome of pregnancy known prior to enrollment).
- Women who have enrolled in the current study with a previous pregnancy.

Cohort 3: Non-Asthmatic Comparison

Inclusion Criteria:

- Currently pregnant women who contact the OTIS Research Center.
- Eligible women may potentially have been exposed to non-teratogenic agents during this pregnancy.
- Women who agree to the conditions and requirements of the study including the interview schedule and release of medical records.

Exclusion Criteria:

- Women who have been exposed to any known teratogenic agents as determined by the OTIS Research Center (list in Annex 1) for any number of days, at any dose, from the first day of the last menstrual period up to and including the end of pregnancy.
- Women with a self-reported diagnosis of asthma, current or previous.
- Women will not be eligible for Cohort 3 if they come in contact with the OTIS Research Center after prenatal diagnosis of a major structural birth defect.
- Retrospective cases (outcome of pregnancy known prior to enrollment).
- Women who have enrolled in the current study with a previous pregnancy.

9.2.1 Modalities of Recruitment

The cohort study will be conducted by investigators at the University of California Research Center for the MotherToBaby/Organization of Teratology Information Specialists (OTIS). The OTIS Research Center conducts the cohort arm of the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) in collaboration with the American Academy of Allergy, Asthma and Immunology (AAAAI). 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 or other forms of electronic 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 source of referrals not only for benralizumab-exposed pregnancies but also for similarly-ascertained pregnant women with a diagnosis of asthma but not treated with benralizumab, and similarly-ascertained pregnant women not diagnosed with asthma who have not used benralizumab nor any known human teratogen.

Other methods of raising awareness about the study include exhibiting at national, regional and local health care professional practice meetings, direct mail to health care providers, and using media, social media, and the MotherToBaby website. Because treatment with benralizumab will require expertise in treating severe asthma, these health care providers will be a particular focus of awareness activities. With the assistance of the AAAAI, providers who treat women with more severe asthma will be a priority target for awareness.

Women who are interested in learning more about the study will be referred to or will self-refer themselves to the OTIS Research Center for information. Those women who are interested and meet the study criteria as described in Section 9.2 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 7 Section 9.6.2. 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 study population by definition consists of volunteers; however, they are expected to represent a wide variety of maternal age, race/ethnic background, and health status (Bakhireva, 2008; Chambers, 1996; Chambers et al., 2013; Chambers et al., 2010). 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. Women under the age of 18 may enroll with parent/guardian consent.

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. Recruitment and enrollment for each cohort group will occur concurrently. Enrollment will be monitored monthly by the OTIS and AstraZeneca team, and adjustments made, if necessary.

Study contact information:
The toll-free phone: [redacted]
Website direct to the pregnancy studies is: https://mothertobaby.org/ongoing-studies/
Home page for the website: www.mothertobaby.org

Table 3 Recruitment Timetable

	Year 1	Year 2	Year 3	Year 4	Year 5
Cohort 1 Benralizumab- exposed group	20	40	55	55	30
Cohort 2 Asthmatic comparison group	30	60	83	83	44
Cohort 3 Non-asthmatic comparison group	30	60	83	83	44

9.3 Variables

9.3.1 Exposure definitions

Benralizumab-exposed cohort: Exposure is defined as any dose of benralizumab for any length of time from 8 weeks prior to LMP through the end of pregnancy, as reported by the mother and validated through medical record review. The 8-week cut-off prior to LMP is based upon the terminal half-life of benralizumab of approximately 15 days (clearance of benralizumab is based on five half-lives).

Exposure is defined as yes/no in the first trimester of pregnancy for major structural birth defects as the primary outcome. For this study, first trimester exposure is defined as any dose between 8 weeks prior to LMP and 13 weeks after LMP. However, exposure to benralizumab in the second (>13 weeks through 26 weeks after LMP) and third trimester (>26 weeks after LMP) will be considered for those selected major birth defects that are potentially biologically plausibly related to later pregnancy exposures, e.g., craniosynostosis. For spontaneous abortion, exposure is defined as yes/no in the first 20 weeks of gestation, and for the other secondary outcomes, exposure is defined as yes/no anytime in pregnancy.

Gestational age is determined by an algorithm using best available information. If 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 dating ultrasound will be used. In the event of absence of any information on dating, the delivery record best estimate of gestational age will be used.

In exploratory analyses, duration of benralizumab use in pregnancy, specific gestational timing, and dose of benralizumab will be explored. In the asthmatic comparison group, duration of other asthma medications use in pregnancy, specific gestational timing, and doses will be explored.

9.3.2 Outcome definitions

- **Major Structural Birth Defects:** a major structural defect is defined and classified using the CDC coding manual (CDC, 2007), as 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 structural defects regardless of etiology. Infant medical records are abstracted by the data coordinator, and reviewed by the study manager. Final validation of the classification of

all major birth defects reported in the study will be conducted by the OTIS Co-Investigator with expertise in the diagnosis of birth defects.

- **Preterm Delivery:** preterm delivery is 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 9.3.1 for further description of the method for defining gestational age and therefore preterm birth.
- **Small for Gestational Age (SGA) Infants:** Live born infants who are ≤10th centile on birth weight, length and/or head circumference for infant sex and gestational age will be considered small for gestational age. The U.S. Centers for Disease Control and Prevention (NCHS) growth charts will be used for full term infants, and preterm growth charts will be used for preterm infants (Lubchenco, 1966). The outcomes of birth weight, length and head circumference are reported by the mother and validated through the medical record.
- **Spontaneous Abortion:** Spontaneous abortion is defined as spontaneous pregnancy loss prior to 20.0 weeks' gestation. In this study, since women enroll after recognition of pregnancy, spontaneous abortions are only identified after enrollment in clinically recognized pregnancies. This outcome is reported by the mother and validated through the medical record.
- **Stillbirth:** Stillbirth is defined as a fetal death that occurs ≥20 weeks' gestation. This outcome is reported by the mother and validated through the medical record.
- **Elective Termination:** Elective termination is defined as deliberate interruption of pregnancy by surgical or medical means.
- **Small for Age Postnatal Growth:** Postnatal growth is measured at approximately 1 year of age among live born infants and age and sex specific percentiles assigned using standard U.S. growth curves. Weight, length and/or head circumference ≤10th centile will be considered small for age. The outcomes of postnatal weight, length and head circumference are collected from pediatric records.

9.3.3 Confounders and effect modifiers

The potential confounders/effect modifiers listed below will be considered in multivariable analyses, 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 birth defect
- Maternal conditions: e.g., depression, diabetes
- Maternal exposures: gestational timing and dose of all over-the-counter and prescription medications, including all asthma medications used during pregnancy; vitamin and

mineral supplements, herbal products; illnesses; fever; vaccinations, travel outside of the U.S.

- Prenatal testing: ultrasound and other prenatal tests; timing in gestation and results
- Pregnancy complications: e.g., pregnancy induced hypertension, gestational diabetes
- Maternal lifestyle habits: cigarette smoking, alcohol consumption and illicit drug use
- Asthma related covariates: Asthma Control Test at each maternal interview, years since diagnosis of asthma, hospitalizations or unscheduled asthma visits for asthma exacerbations throughout pregnancy, use of systemic steroids for asthma exacerbations, and classification of asthma severity at enrollment based on women self-reported prescription classified by (GINA guidelines, 2016) guidelines.

Methods for identifying and controlling for these confounders and/or effect modifiers are described in Section 9.7.1. The Statistical Analysis Plan (SAP) will provide greater detail on the definitions of, the identification of and the controlling for confounders and/or effect modifiers.

9.4 Data sources

Maternal Interviews: In all three study groups, data are collected by semi-structured maternal telephone interview on two to four occasions during, and shortly after completion of pregnancy. The interviews include data on exposure timing, dose, and duration for all medications, including benralizumab, taken anytime in pregnancy as well as data on a wide variety of confounders (See Section 9.3.3).

For women exposed to benralizumab or other asthma medications, information on disease severity/symptom control from the Asthma Control Test is obtained directly from the mother at each maternal telephone interview. In addition, information on asthma related hospitalizations and physician visits is collected at the enrollment interview and each of the subsequent maternal interviews. 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. At this time point the Asthma Control Test questions are asked again to reflect the last four weeks of pregnancy. In addition, asthma treatment regimen at first day of last menstrual period for the current pregnancy according to GINA guidelines will be used to classify disease severity.

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 allergist/ pulmonologist, hospital of delivery, pediatrician, and other health care provider specialists involved in the pregnancy. These records are abstracted and used to validate pregnancy outcomes, collect information on health and growth of the child, and when necessary to provide details regarding timing or dose of benralizumab and other asthma medications in the absence of clear information from maternal report. Self-reported prescriptions used for GINA

classification will be validated with medical record information where available. Pre-defined definitions for each of the study outcomes are used for classification.

Validation of final classification of major birth defects, the primary outcome, that have already been identified by the study Data Coordinator and verified and classified by the Study Manger, is conducted periodically and before each annual and final study report by the study Co-Investigator, a specialist in dysmorphology/teratology.

Table 4 Variables collected per cohort

Variable	Cohort 1 Benralizumab-exposed	Cohort 2 Asthmatic comparison	Cohort 3 Non-Asthmatic comparison
Maternal Interviews			
Exposure timing[1]	√	√	√
Dose[1]	√	√	√
Duration of medications[1]	√	√	√
Confounders/effect modifiers	√	√	√
Disease severity (ACT & asthma treatment regimen)	√	√	X
Asthma related hospitalizations and physician visits	√	√	X
Pregnancy outcome	√	√	√
Birth defects	√	√	√
Pregnancy complications	√	√	√
Infant complications	√	√	√
Infant size	√	√	√
Medical Record Abstraction[2]			

Variable	Cohort 1 Benralizumab-exposed	Cohort 2 Asthmatic comparison	Cohort 3 Non-Asthmatic comparison
Pregnancy validation	√	√	√
Pregnancy outcome validation	√	√	√
Exposure timing validation[1]	√	√	√
Dose validation[1]	√	√	√
Self-reported prescription validation[1]	√	√	√
Major structural birth defects[3]	√	√	√

[1]For cohort 1 & 2 primarily asthma medication will be assessed. For all three cohorts medical records will be used to verify exposure information where data is missing or discrepant.

[2] Information will be dependent on the completeness of the medical record

[3]Performed periodically and before each annual and final study reports

9.5 Study size

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

- 200 women exposed to benralizumab at any time 8 weeks prior to LMP and throughout pregnancy
- 300 women with treated asthma, unexposed to benralizumab, aiming to represent the full spectrum of asthma severity with emphasis on severe patients
- 300 non-asthmatic comparison women

The sample size is considered plausible based on the experience of the OTIS research group with previous studies of asthma in pregnancy, but enrollment rates for the current study are unknown. Although it is unknown to what extent benralizumab will be used by pregnant women, experience with recruitment in the omalizumab (Xolair) EXPECT registry provides some support for the proposed sample size. In six years of recruitment, the EXPECT registry recruited 191 exposed pregnancies (J. Namazy et al., 2015).

No formal statistical hypothesis testing will be done. Point estimates of the rate ratios and associated CI's between the benralizumab exposed cohort and the unexposed cohorts will be used to evaluate the potential risk of benralizumab to mothers and fetuses.

Table 5 is included to contextualize the magnitude of reported relative risks. This outlines the probability of observing rate ratios in excess of different thresholds either by chance (i.e., when the true underlying risk ratio is 1) or when there is a true underlying increase in risk (RR of 1.2, 1.5 or 2), given the planned sample size.

- If the truth is that there is no increase in risk (true RR=1), the current study would have a relatively small probability (<20%) of reporting out an observed relative risk of 1.5 or greater.
- If the truth is that there is a doubling of risk, the current study would have a higher probability of reporting an observed RR greater than 1.5 (≥ 70%), and a smaller probability of reporting out an observed RR < 1.2 (≤13%).

Table 5 Probability that observed relative risk point estimates (exposed/unexposed) will exceed different thresholds

Outcome	Prevalence in unexposed cohort	Expected number of Exposed/ Unexposed Asthmatic cohorts		True RR	Probability observed RR exceeds X			
		enrolled	with complete outcome		X=1.2	X=1.5	X=2.0	X=3.0
All major birth defects in live born infants	3%	200/300	180/270	1	0.38	0.19	0.10	0.02
				1.2	0.51	0.29	0.16	0.04
				1.5	0.68	0.45	0.27	0.08
				2	0.87	0.70	0.49	0.18
Preterm birth	7%	200/300	180/270	1	0.30	0.10	0.02	0.00
				1.2	0.50	0.22	0.06	0.00
				1.5	0.76	0.47	0.18	0.02
				2	0.96	0.83	0.49	0.08
SGA infant	10%	200/300	180/270	1	0.26	0.07	0.01	0.00
				1.2	0.49	0.19	0.03	0.00
				1.5	0.81	0.48	0.13	0.00
				2	0.99	0.88	0.50	0.05

Numbers in Table 5 are based on 90% of enrolled pregnancies ending in live birth with completed outcome. The effect size for all birth defects among live births is based on a prevalence of 3% in the asthmatic comparison group. The effect size for preterm birth is

based on a prevalence of 7% in the asthmatic comparison group (Bakhireva, 2008). The effect size for small for gestational age infants (SGA) is based on a prevalence of 10% in the asthmatic comparison group. Simulations were done using R to estimate the probabilities presented in Table 5.

It is projected, based on experience with the EXPECT registry that almost all benralizumab-exposed participants will have received at least one dose of the medication in the period of time from eight weeks prior to LMP to the end of the trimester and will be eligible for analysis of major structural birth defects. It is also expected that the majority of study participants will enroll in the study upon recognition of pregnancy in the first trimester; however, some will enroll after 20 weeks' gestation and therefore will not be included in the analysis of spontaneous abortion.

9.6 Data management

Maternal interviews are conducted at enrollment and up to two additional time points, depending on the gestational age at enrollment. An outcome interview is conducted by telephone after the end of pregnancy, typically within 4-6 weeks after the estimated date of delivery (EDD). Medical records are requested from the delivery facility (maternal and neonatal information), obstetric provider (maternal information), pediatrician (neonatal/infant) and any specialty physician (maternal and neonatal/infant information). Data are abstracted from medical records using a standard abstraction form, and this information is entered into the study database by trained personnel. Hard copies of all study forms and hard copies and/or electronic copies of medical records are retained in the OTIS Research Center at the University of California San Diego.

9.6.1 Data handling conventions

Initial identification of major structural defects is performed by the study Data Coordinator, and then verified and classified by the Study Manager using the CDC coding manual (CDC, 2007). Final validation of the classification of all major birth defects reported in the study will be conducted by the OTIS Co-Investigator with expertise in the diagnosis of birth defects. 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, small for gestational age infants, and postnatal growth.

Lost-to-follow-up status is designated if a participant withdraws from the study before the outcome of pregnancy is known or reported, or if 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. Participants who are lost-to-follow-up but who have at least one day of follow-up after enrollment are included in time-to-event outcomes such as spontaneous abortion if they are otherwise eligible for inclusion in that analysis.

Table 6 Denominators by outcome

Outcome	Denominator
Major Structural Birth Defects Among Live Births	Pregnancies ending in live birth with exposure in the first trimester for benralizumab cohort, and other comparison groups at least one malformed infant in an individual pregnancy is considered one malformed outcome
Major Structural Birth Defects Among All Pregnancies	Pregnancies with any outcome excluding those lost-to-follow- up; with exposure in the first trimester for benralizumab cohort, and other comparison groups; at least one malformed fetus/infant in an individual pregnancy is considered one malformed outcome
Spontaneous Abortion	Pregnancies enrolled in the study prior to 20.0 weeks' gestation with at least 1 follow-up data collection point after enrollment date. Exposure can occur any time in pregnancy prior to the event.
Preterm Delivery	Pregnancies enrolled prior to 37.0 weeks' gestation and ending in at least one live born infant. Excludes twins or higher order multiples due to inherent higher risk of preterm birth in multiples. Exposure can occur any time in pregnancy prior to the event.
Small for Gestational Age Infants	Pregnancies ending in at least one live born infant; excluding twins or higher order multiples due to the inherent higher risk of reduced birth size in multiples. Exposure can occur any time in pregnancy prior to the event.
Still birth	All pregnancies, excluding lost-to-follow-up. Exposure can occur any time in pregnancy prior to the event.
Elective Termination	All pregnancies, excluding lost-to-follow-up. Exposure can occur anytime in pregnancy prior to the event.
Postnatal Growth	Pregnancies ending in at least one live born infant with pediatric growth records available at approximately 1 year of age. Multiples are excluded. Exposure can occur anytime in pregnancy.

Coding of outcomes is performed by the study staff using the definitions provided in the protocol. Interview, diary, and examination data will be recorded on hardcopies of forms, medical records and medical record abstraction forms may be recorded on hardcopies or electronically; these records will be retained in the Coordinating Center. Data from all forms will be extracted and entered into a customized database located in the Coordinating Center. The data will be extracted and entered by trained study personnel with extensive experience with this type of information. Entries will be periodically reviewed for logical errors, and intake and outcome forms will be validated for data entry accuracy.

The primary source for information collected on demographics and exposures is by maternal interview, as the participant typically provides more accurate information than the medical records, especially in regards to non-prescription medications and any medications not taken as prescribed. Doses, dates, and timing of exposure are confirmed with medical records. If the medication is administered in the office, the medical record is the primary source; if the medication is administered at home and there is a discrepancy between the record and maternal report, the participant is contacted and asked about the discrepancy.

The medical record is the primary source for type of prenatal test, date, and results of prenatal tests, disease diagnosis, and infant outcomes, including birth and postnatal growth, and major structural defects.

Data included in the interim reports is cumulative, therefore data may change when additional information is received either by maternal report or by medical records.

The method and duration of storage of data is addressed in the informed consent. Access to the database will be controlled by password. Hardcopies of participant files, original oral consent signed and dated by the interviewer, signed consent forms, and original signed medical record release forms will be kept in a locked file room, in locked cabinets, and scanned into an electronic file, under the supervision of the OTIS Research Center.

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

9.6.2 Timings of assessment during follow-up

Table 7 Timing of cohort enrollment, interviews, medical record requests and review*

	Anytime in Pregnancy	20-22 weeks' gestation*	32-34 weeks' gestation	0-6 weeks post-delivery	0-12 months post-delivery
Contact / Referral	√				
Enrollment and Consent	√				
Intake Interview	√				
Interim Interview I		√			
Interim Interview II			√		
Outcome Interview				√	
Medical Record Release Forms Sent for Signature				√	√

*A participant may have anywhere from 1-3 interviews during pregnancy, with a minimum of 4 weeks between interviews. If a participant enrolls at 18 weeks, the 20 week interview will be scheduled at 22 weeks. If a participant enrolls between 19 weeks and 30 weeks, the next scheduled interview will be 32 weeks. If a participant enrolls at 30 weeks, the 32 week interview will be scheduled at 34 weeks. If a participant enrolls after 30 weeks, no additional interviews will be scheduled during pregnancy.

9.7 Statistical analysis

9.7.1 Main analysis

A detailed Statistical Analysis Plan (SAP) will be prepared and finalized prior to the submission of the first interim report.

Primary Endpoint:

The primary endpoint will be major structural defects among live born infants.

The primary comparison will be between the first-trimester benralizumab-exposed group and the disease cohort receiving asthma treatment anytime in pregnancy.

Secondary comparisons for major structural birth defects will be conducted within the subgroup of pregnancies ending in live birth, spontaneous abortion, stillbirth or elective termination, excluding lost-to-follow-up, comparing first-trimester benralizumab-exposed to the treated disease cohort.

Additional secondary comparisons will be made between the first-trimester benralizumab-exposed group and the treated asthma and non-asthmatic cohort, and between the treated asthma and non-asthmatic cohorts. Further details will be specified in the SAP.

Secondary Endpoints:

Preterm Delivery: After exclusion of twins or higher order multiples, the proportion of pregnancies ending in live birth <37 weeks' gestation will be compared between the benralizumab group enrolled and exposed anytime in pregnancy prior to 37.0 weeks' gestation and the treated diseased and non-diseased cohorts enrolled prior to 37.0 weeks' gestation.

Small for Gestational Age Infants: After exclusion of twins or higher order multiples, the proportion of pregnancies ending in a live born infant ≤10th centile of birth weight, length and/or head circumference will be compared between the benralizumab group exposed anytime in pregnancy and the treated diseased and non-diseased cohorts.

Spontaneous Abortion: For those women in all three cohorts who enrolled in the study prior to 20.0 weeks' gestation, the proportion of pregnancies ending in spontaneous abortion accounting for left truncation will be compared between those in the benralizumab group enrolled and exposed any time in pregnancy prior to 20.0 weeks' gestation and those in the treated diseased and non-diseased cohorts.

Stillbirth: The proportion of pregnancies ending in stillbirth will be compared between those in the benralizumab-exposed group and those in the treated diseased and non-diseased cohorts.

Elective Termination: The proportion of pregnancies ending in elective termination will be compared between the benralizumab exposed group enrolled prior to 20.0 weeks' gestation, and the diseased and non-diseased cohorts enrolled prior to 20.0 weeks' gestation.

Small for Age Postnatal Growth: After exclusion of twins or higher order multiples, the proportion of pregnancies ending in a live born infant ≤10th centile of postnatal weight, length and/or head circumference will be compared between the benralizumab group exposed anytime in pregnancy and the treated diseased and non-diseased cohorts.

Statistical methods:

Descriptive tables will be prepared for characteristics of each of the cohorts in each interim and final report displaying n, means, standard deviations, minimums and maximums or proportions and percentages.

For the primary endpoint of major structural defects, and for the secondary endpoints of small for gestational age infants, postnatal growth and elective termination, un-adjusted relative risk estimates will be presented together with exact two-sided 95% and 80% confidence intervals.

For the secondary endpoints of preterm delivery, spontaneous abortion, and stillbirth, survival methods will be used (Kaplan Meier) to estimate crude rates and confidence intervals accounting for gestational timing of enrollment in the study.

Adjusted analyses producing relative risks and 95% and 80% confidence intervals or hazard ratios and 95% and 80% confidence intervals, where numbers permit, will be conducted. A minimum of 30 events in the overall analysis sample is required for adjusted analysis for those outcomes assessed with logistic regression. A minimum of 20 events in the overall analysis sample is required for adjusted analysis for those outcomes assessed with Cox Proportional Hazards.

Confounders will be considered for each adjusted analysis separately, using the method of change in estimate of the effect of exposure to benralizumab by 10% or more. If one confounder is identified, direct adjustment will be performed. However, given the expected low frequency of events in a study of this size, if two or more confounders are identified in any given analysis, a propensity score approach for adjustment will be considered. Appropriateness of models will be assessed graphically and by standard statistical methods.

9.7.2 Exploratory/sensitivity analyses

Exploratory analyses addressing potential effect modifiers such as Asthma Control Test measures of disease symptom control, and measures of asthma exacerbation will be addressed.

In addition, sub-analyses based on length and gestational timing as well as dose of exposure to benralizumab will be performed.

Stratified analyses based on prenatal diagnostic test performed prior to enrollment in the study will be conducted for the primary endpoint. The purpose of this analysis is to address the inherent bias in excluding women at the time of enrollment in the cohort study who have already received prenatal diagnosis of a major structural birth defects, but including women who have already had a normal result or prenatal diagnosis for major structural birth defects prior to enrollment. Therefore, the planned stratified analysis will compare the birth prevalence of major structural birth defects among the subset of women enrolled in the cohorts prior to prenatal diagnostic testing to detect structural defects (ultrasound for structure, chorionic villus sampling, amniocentesis), to the birth prevalence of major birth defects among the subset of women enrolled in the cohorts after prenatal diagnostic testing to detect structural defects.

Regarding asthma severity, the measures are only captured after enrollment, and in the exposed group only after being on treatment, so they would typically not be included in the analysis as adjustment factors as they could be mediators. However, descriptive analyses of the balance in cohorts on measures of disease severity are presented. Sub-analyses or

sensitivity analyses within disease severity categories can be performed, depending on the distribution of the covariates. This would be described in detail in the SAP.

Sub-analyses excluding chromosomal or known genetic anomalies (classified by study investigators as having a known genetic etiology) will also be conducted. Details will be provided in the SAP.

9.7.3 General considerations for data analyses

The general approach to controlling for confounding is to evaluate each relevant confounder (from a pre-specified list for each outcome) to determine if inclusion of the confounder in a model containing exposure to benralizumab changes the estimate of the effect of exposure by 10% or more. The confounders will be assessed univariately and those confounders that are identified as meeting criteria described above are incorporated into multivariate analyses as described in the statistical analysis Section 9.7.1, if sample size permits. Further details will be contained in the SAP. Control for confounding by indication is addressed by comparison to the treated disease group. However, as described in exploratory analyses in Section 9.7.2, attention to measures of disease symptom control and underlying severity will also be addressed by subgroup and stratified analysis.

9.7.4 Assessment of cases for a signal of major structural birth defects

An aggregate assessment of cases with major structural birth defects will be conducted at each interim report and for the final report for the study. This assessment will be conducted by the investigators and reviewed by the Scientific Advisory Board members. The assessment will consist of the following steps:

1 a review of specific birth defects for any evidence of a cluster of similar multiple malformations, or clusters of similar isolated major birth defects among exposed pregnancies that does not occur in the comparison pregnancies;
2 a review of alternative aetiologies for the specific birth defects clusters, such as family history or co-exposures;
3 a review of the biologic plausibility of the gestational timing of exposure to the medication relative to the embryologic timing of initiation of the specific birth defect(s);
4 a review of the cumulative published literature for any evidence consistent with the occurrence of that cluster of defects with exposure to the medication in pregnancy.

9.8 Quality control

As noted in Section 9.6, 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 Standard Operating Procedures, and validation of data entry for critical study variables is conducted for 100% of study maternal interviews. Data exported for interim reports and final

analyses for this study are checked for logical errors, and range checks are performed. All major structural birth defect classifications are verified by the study investigators. Data are reviewed on an interim basis by the VAMPSS external advisory committee (See Section 12.1.2). Final data sets are cleaned and utilized for preparation of the analyses and study reports. All analyses (coding and output) are reviewed by the OTIS Research Center 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.

9.9 Limitations of the research methods

Potential limitations of the research methods include:

The study relies on a volunteer sample which may or may not be entirely representative of all women who take benralizumab during pregnancy. However, for a new product used for a relatively rare condition this is likely 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 more severe asthma, to increase awareness about the study.

It is unknown what the distribution of gestational timing of exposure will be in the benralizumab-exposed cohort. In the EXPECT registry for omalizumab, pregnancy exposures were predominately limited to the first trimester (J. Namazy et al., 2015). Therefore, it is possible that the study will only be able to address the risks or safety of exposures that occur in the first few weeks of pregnancy before women typically recognize that they are pregnant.

The sample size that is achievable for a new product used for a relatively rare condition limits the power to detect differences, especially for rare outcomes such as major structural 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 these types of pregnancy exposure studies. However, based on expected gestational timing of enrollment, spontaneous abortion rates in late first trimester and early second trimester will be able to be addressed.

As this study does not involve matching on disease severity, it is possible that the exposed and disease-matched groups may differ on this factor. Measures of disease severity/symptom control will be captured in the study. This will allow for altering of recruitment emphasis as the study progresses to ensure that there is appropriate balance in severity between groups.

It is also possible that other exposures, as well as differences in treatment patterns among the various health care providers treating participants could be important confounders. Depending

on sample size or availability of data on these covariates, not all of these variables may be controlled in multivariable analyses.

It is also possible given the limited sample size that by chance a false positive association may be detected. In this context, the review for evidence of a pattern of major structural defects, and for a pattern of adverse outcomes associated with exposure will be used to help with interpretation of results.

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 benralizumab-exposed pregnancies as well as appropriate comparison group pregnancies, and the OTIS research group has an excellent participant retention rate (<5% lost to follow-up). In addition, the study design allows for appropriate comparison to a treated disease group, and for appropriate attention to confounding or effect modification.

9.9.1 Study closure/un-interpretability of results

In consultation with the VAMPSS Scientific Advisory Committee, 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 ranging from 20-55 patients exposed to benralizumab per year. Regular review of enrollment numbers will be performed and numbers compared to the sponsor's data and other external data on the uptake of benralizumab to determine if uptake 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 benralizumab they may withdraw from the study upon written notification.

9.10 Other aspects

None

10. PROTECTION OF HUMAN SUBJECTS

10.1.1 Institutional Review Board / Ethics Committee

According to the FDA Guidance document, registries such as this must comply with ethical principles and regulatory requirements involving human subjects research. Therefore, this

protocol and informed consent documents must be approved by the Institutional Review Board (IRB) at the University of California, San Diego. The chairman or the recording secretary of the IRB must have signed a form indicating approval. Notification of the Board's approval of the study must be provided to the Sponsor prior to initiation of participation in the Registry.

10.1.2 Ethical conduct

This Registry will be conducted in compliance with the protocol, International Society for Pharmacoepidemiology's Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the United States, U.S. FDA regulatory requirements, in accordance with the ethical principles of the Declaration of Helsinki (1995), and the HIPAA (Health Insurance Portability and Accountability Act) (HHS, 2002, 2003; ISPE, 1996).

10.1.3 Informed consent

10.1.3.1 Oral and written consent

The pregnant woman must agree to the oral consent form at the time of enrollment and before completing the intake interview. She must also sign for release of medical information and the HIPAA authorization (when applicable) to allow the study staff to obtain information on the pregnancy and the pregnancy outcome from the participant's obstetric provider, the delivery hospital, any healthcare specialist treating her indicated disease, and the infant's pediatric provider.

The original oral and signed informed consent documents, HIPAA authorizations, and medical record release forms will be stored and maintained by the OTIS Research Center. These medical record release documents are in the authorized format required by the University of California, San Diego and are compliant with HIPAA regulations.

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 and written assent from themselves prior to the initial intake interview. Consent/assent forms and study participation materials are available in English or Spanish.

10.1.4 Participant confidentiality

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

OTIS 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 current human subjects research training, and are listed individually as authorized to have access to the study data on the study IRB-approved research plan. Final study data files used by the investigators for analysis are stripped of identifiers and archived at the OTIS Research Center without personal identifiers.

Sponsor representatives through the Scientific Advisory Committee have access to de-identified summary data as part of the periodic annual and the final study reports.

Care will be taken to ensure that no individual participant is identifiable in the data tables published in the annual interim or final reports, or other presentations or publications.

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 purpose of the Benralizumab Pregnancy Exposure Study is to monitor planned and unplanned pregnancies exposed to benralizumab and to evaluate the possible teratogenic effect of this medication. For benralizumab-exposed pregnancies predefined specific pregnancy outcomes that are classified as serious adverse events (SAE's) will be identified and reported. These selected SAEs include major structural birth defects, spontaneous abortion, stillbirth and neonatal death, and maternal death. These events will be reported to the sponsor's safety department within 24 hours of awareness.

Tata Consultancy Services (TCS) will be responsible for processing all SAEs (as above) onto the AZ global safety database.

The following contract information should be used:

1 Clinical trial mailbox should be used: Clinical Trial (TCS) - [redacted]
2 The sponsor's safety department hotline for all adverse event reports is [redacted].
3 In the event of a secure email link being unavailable the following fax number should be used: Fax number [redacted]

If during the study, the OTIS Research Center investigators become aware of an adverse event explicitly attributed to benralizumab by the participant or her health care provider, this will also be reported to the sponsor's safety department within 24 hours of awareness. The participant will be asked if she is willing to release her contact information, or the contact information for her health care provider for follow-up by the sponsor.

Any pregnancies in women exposed to benralizumab reported to the OTIS Research Center retrospectively, or who otherwise do not meet the study eligibility criteria, will be referred to the Sponsor.

The interim and final study reports will include summary tables and analyses for each of the study endpoints as part of the research questions being addressed.

The selected SAEs of interest in this study include major structural birth defects, spontaneous abortions, elective terminations, stillbirths, neonatal deaths and maternal death in the benralizumab exposed group. The method of causality assessment of the adverse events collected in this study will include the following actions:

MotherToBaby OTIS pregnancy studies will be forwarding these SAEs to AstraZeneca for case processing and reporting within 24 hours of awareness. MotherToBaby OTIS pregnancy studies will not be providing causality assessment for the SAEs. AstraZeneca will be providing company causality assessment and will be responsible for expedited reporting. Every reported serious adverse event will undergo a formal causality assessment that will involve assessing the case as valid and reviewing each case based on medical judgement and global introspection. Using the causal criteria of temporality, biological plausibility (consistency with known drug mechanism of action and safety profile), relevance, absence of confounding factors (e.g. excluding other known human teratogens), lack of alternate etiology and consistency with current medical knowledge, each serious adverse event is reviewed by a group of senior experienced patient safety professionals. Causality of 'related' is made if following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

Causality assessment by AstraZeneca will accompany each case reported to the regulatory agencies. An alternate aetiology or explanation will be provided in cases where causality is negative.

AstraZeneca will conduct signal detection activities as part of their routine safety surveillance processes. This is in addition to the planned analyses for each of the study endpoints conducted as part of the research questions being addressed (see section 9.7.4).

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report describing the study endpoints will be prepared by the OTIS Research Center and provided to the Sponsor. The Sponsor will communicate the results to the FDA, the European Medicines Agency (EMA), and any other relevant regulatory authorities.

12.1.1 Ownership and Use of Data and Study Results

The individual level study data is owned by OTIS, but in the circumstance that the Regulatory Health Authorities (e.g. EMA, FDA) requests individual level data, the de-identified dataset will be provided.

12.1.2 Scientific Advisory Committee

The VAMPSS Scientific Advisory Committee will have full access to the interim reports and the final study report. Specific requests from the Committee for additional analyses or clarifying questions will be addressed by the OTIS Research Center.

This committee consists of representation from the U.S. Centers for Disease Control and Prevention, Center for Birth Defects and Developmental Disabilities; the Eunice Kennedy Shriver National Institute of Child Health and Development; a biostatistician; a consumer representative; and disease-specific specialty representatives. 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.

12.1.3 Publications

Publications including manuscripts on the study outcomes will be prepared by the study investigators and provided to the Sponsor for comment. Manuscripts will be provided for comment at least 45 days in advance of planned submission. Abstracts and presentations will be provided for comment at least 30 days prior to planned submission.

The study investigators will initiate presentations at scientific and professional meetings. The OTIS Research Center will use these meetings and several other strategies to raise awareness of the study.

- Interim Reports: An interim report will be issued to the Sponsor and the Scientific Advisory Committee on an annual basis in conjunction with the annual Advisory Committee meeting. Each issue will contain historical information as well as new data, and therefore will supersede all previous reports. The report will describe the experience of the ongoing study, summarize data collection and provide descriptive data on pregnancy outcomes.
- Website: Information on the study is incorporated into the existing OTIS/MotherToBaby website that includes a description of the study, contact information, enrollment eligibility and instructions. The study will be added to the FDA Pregnancy Registry website. The study will be posted to ClinicalTrials.gov. There are other websites that may provide study contact information.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Table 8 List of stand-alone documents

	Document reference number	Date	Title
1	N/A	21 November 2017	Known Human Teratogen

KNOWN HUMAN TERATOGENS – DISQUALIFIERS FOR NON-DISEASED CONTROLS FOR ALL MTB STUDIES:

*For most known teratogens, exposure between LMP and conception is not disqualifying, so consider **post-conception** exposure only. Exceptions: acitretin and etretinate (see notes next to these exposures).*

Exposure	**Notes**
ACE Inhibitors	Class of medication used to treat high blood pressure
Acitretin	Any exposure **within 2 years** of LMP.
Alcohol, Heavy	**>5 drinks per week or ≥ 5 drinks in 1 day: Week = Sun-Sat** If MOB gives an estimated range of number of drinks, eligibility is based on the maximum.
Aminopterin	
Antiseizure / Anticonvulsant Medications	
Antineoplastics, Other	Drugs used for the treatment of cancer
Cocaine	
Cytomegalovirus (CMV)	
Type I and Type II Diabetes	Type II Diabetes also listed below
Etretinate	Any exposure **within 10 years** of LMP.

Fever, High	**102 degrees or higher for 24 hours or longer – please ask if fever broke or was consistent**
Fluconazole, Systemic	**≥7 days total** (consecutive or non-consecutive) *need to ask if the woman is planning on taking again during pregnancy*
Isotretinoin	
Lenalidomide	
Lithium	
Methimazole	
Methotrexate	
Propylthiouracil (PTU)	
Radiation, High Dose	≥ 5 rads to the uterus
Rubella	
Thalidomide	
Toxoplasmosis	
Varicella	Primary case of chicken pox
Warfarin (Coumadin, Jantoven) derivatives	

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: The Benralizumab Pregnancy Exposure Study: A VAMPSS Post-Marketing Surveillance Study

Study reference number: D3250R00026

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6.0
1.1.2 End of data collection[2]	☒	☐	☐	6.0

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.3 Study progress report(s)	☒	☐	☐	6.0
1.1.4 Interim progress report(s)	☒	☐	☐	6.0
1.1.5 Registration in the EU PAS register	☒	☐	☐	6.0
1.1.6 Final report of study results.	☒	☐	☐	6.0

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8.0
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.0
2.1.2 The objective(s) of the study?	☒	☐	☐	8.0
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	9.1
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.5
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.5

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.0

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.1, 9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2
4.2.2 Age and sex?	☒	☐	☐	9.2
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☒	☐	☐	9.1
4.2.5 Duration of follow-up?	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.4
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.0
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.4, 9.6.1
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7.1
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7.2
7.2 Does the protocol address:	☒	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.9

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.1

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.6.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.6.1
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7.1
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.3 Are stratified analyses included?	☒	☐	☐	9.7.2
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.3

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.6.1
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6.1
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12.1.2

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.9

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1.1

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.0

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5.0

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.0
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.1.3

Comments:

Name of the main author of the protocol: Christina Chambers

Date: 05 Sep 2018 [redacted]

Signature: [redacted]