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

The following guiding principles have been applied to the disclosure:

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

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

NON-INTERVENTIONAL SAFETY STUDY REPORT

Study title: The Mepolizumab Pregnancy Exposure Study: a VAMPSS post marketing surveillance study of Mepolizumab safety in pregnancy

Study number: 200870

Version number: Version 1

Report Date: 22 July 2024

Signature page

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MAH (Marketing Authorization Holder):

Role	PPD Immunology and Emerging Epidemiology	**Printed Name**	PPD
Signature	PPD	**Date (DD-MMM-YYYY)**	22-Jul-2024
Role		**Printed Name**	
Signature		**Date (DD-MMM-YYYY)**	

Investigator:

By signing below, the investigator acknowledges that he/she has read and understands this report, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study has been conducted according to all requirements as defined in the study protocol, Trial Agreement, good pharmacovigilance practices, and all applicable regulatory requirements. If applicable, he/she has complied with the requirements for obtaining informed consent from all study patients prior to having initiated any protocol-specific procedures and for having obtained written initial and ongoing ethics committee(s) protocol review and approval.

Role	Principal Investigator	**Printed Name**	Professor Christina Chambers, PhD, MPH
Signature		**Date (DD-MMM-YYYY)**	

NON-INTERVENTIONAL SAFETY STUDY
STUDY REPORT

Study information

Title	The Mepolizumab Pregnancy Exposure Study: a VAMPSS post marketing surveillance study of Mepolizumab safety in pregnancy
Protocol number	200870
Version identifier of the study report	Version 1.0
Date of study report	22 July 2024
EU PAS register number	EUPAS13772
ClinicalTrials.gov ID	Not Applicable
Active substance	Mepolizumab
Medicinal product	Nucala
Product reference	Mepolizumab
Procedure number	
Joint PASS	No
Research question and objectives	To monitor planned and unplanned pregnancies exposed to mepolizumab and to evaluate the possible teratogenic effect of this medication relative to the pregnancy outcomes of major birth defects, preterm delivery, small for gestational age infants and spontaneous abortion or stillbirth.
Country(-ies) of study	United States (US) and Canada
Author	PPD , PhD, MPH Department of Pediatrics University of California San Diego, 9500 Gilman Drive MC 0828, La Jolla, CA 92093
Marketing authorization holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
MAH Contact Person	PPD Global Regulatory Affairs Lead Respiratory Therapeutic Group Global Regulatory Affairs GlaxoSmithKline Research & Development Ltd

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1.0 ABSTRACT

Title: The Mepolizumab Pregnancy Exposure Study: a VAMPSS post marketing surveillance study of Mepolizumab safety in pregnancy

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 do not adequately respond to current standard therapy. Mepolizumab (NUCALA™) is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 6 years and older, and with an eosinophilic phenotype, and is given as 100 mg by subcutaneous injection every four weeks. Mepolizumab may be utilized by pregnant women when they and their doctor believe the risk benefit favors its use. Also, given the long half-life, inadvertent exposure in pregnancy is likely, even upon immediate cessation of treatment once pregnancy is suspected or confirmed. A pregnancy exposure cohort study to assess the safety of mepolizumab in pregnancy was initiated. Information regarding the safety of mepolizumab in human pregnancy is essential from a public health perspective to help inform clinical practice.

Research question and objectives: The purpose and objectives of the study were to monitor planned and unplanned pregnancies exposed to mepolizumab and to evaluate the possible teratogenic effect of this medication relative to the pregnancy outcomes of major birth defects, preterm delivery, small for gestational age infants and spontaneous abortion or stillbirth.

Study design: This was a prospective, observational, exposure cohort study of pregnancy outcomes in women exposed to mepolizumab during pregnancy compared to pregnancy outcomes in women with a diagnosis of asthma who have not used mepolizumab during pregnancy but have used other anti-asthmatic medications (treated disease comparison group), and pregnancy outcomes in women not diagnosed with asthma (non-disease comparison group).

Population: The study population consisted of three cohorts: 1) a mepolizumab-exposed cohort with exposure to at least one dose of the drug from 8 weeks prior to the first day of the last menstrual period to the end of pregnancy; 2) a disease cohort with treated asthma who have not been exposed to mepolizumab within 8 weeks prior to the first day of the last menstrual period or throughout pregnancy; 3) a non-asthmatic cohort who have no current diagnosis of asthma and have not been exposed to any known human teratogen but may have potentially been exposed to non-teratogenic agents.

Variables: Exposure was defined as mepolizumab treatment by maternal report and verified by medical record review. Outcome variables included major birth defects, spontaneous abortion, stillbirth, preterm delivery, and small for gestational age. These were obtained by maternal report and verified by medical record review. Potential confounders or covariates collected include 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 and symptom control.

Data sources: Information was 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.

Study size: The target sample size for the study was 200 women in the mepolizumab-exposed cohort; 300 women in the treated disease cohort; and 300 women in the non-asthmatic cohort.

Statistical method: Demographic and baseline characteristics were compared between the cohorts. The analysis was descriptive only due to the low number pregnancies enrolled in the mepolizumab-exposed

cohort. Prevalence or incidence estimates for the primary and secondary outcomes of the study were calculated with their 95% confidence intervals.

Milestones: The study was planned for 6.5 years from start of enrollment (first patient in (FPI) to study completion). Five years of active recruitment was originally planned, with an CCI report reviewed by the Scientific Advisory Committee each year.

Results: This final report is a composite of cumulative pregnancy data for women enrolled between 03 November 2016 and 21 November 2022.

Of the 291 participants enrolled in this prospective cohort study, 23 were enrolled in the mepolizumab-exposed cohort, 136 in the disease-matched unexposed cohort, and 132 in the non-diseased unexposed cohort.

Among the mepolizumab-exposed pregnancies that were enrolled in the cohort, excluding those lost to follow-up, there were 2/17 with a major birth defect (relative to 8/111 in the disease-matched unexposed cohort and 8/109 in the non-diseased matched unexposed cohort) (Table 4), one spontaneous abortion (relative to 2/63 in the diseased-matched unexposed cohort and none in the non-diseased unexposed cohort) (Table 5), and among pregnancies ending in liveborn singletons, no preterm deliveries (relative to 8/105 in the diseased-matched unexposed cohort and 7/96 in the non-diseased unexposed cohort) (Table 6). By definition, approximately 10% of infants were expected to meet the criteria for small for gestational age (SGA) at delivery due to the normal distribution of infant size. In the mepolizumab-exposed cohort, >10% of liveborn singletons were SGA on weight and head circumference: 2/15 infants SGA on weight and 1/6 on head circumference. In the disease-matched unexposed cohort, >10% of liveborn singletons were SGA on head circumference: 10/81 infants SGA on head circumference. In the non-diseased unexposed cohort, no infants were >10% SGA on weight, length or head circumference measurements (Table 8). For postnatal growth at approximately 1-year, 1/5 children in the mepolizumab cohort were small for age for postnatal weight and length. In both comparison groups, the proportion of small infants at about 1 year of age exceeded the 10 % expected in the general population on weight, but did not on length or on head circumference (Table 8). There were no stillbirths in the mepolizumab-exposed cohort (1 in the non-diseased unexposed cohort). There was 1 elective termination in the mepolizumab-exposed cohort (compared to none in either the diseased unexposed cohort or the non-diseased unexposed cohort) (Table 3).

Discussion: Due to the small sample size of mepolizumab-exposed pregnancies in this study, the findings are limited in interpretability. There was no evidence of a pattern of major birth defects in pregnancies exposed to mepolizumab, there were no stillbirths, one spontaneous abortion, and one termination reported in the exposed cohort. In summary, no patterns were detected; however, the sample size was too small to draw conclusions about safety in pregnancy.

Marketing Authorization Holder(s)

Names and Affiliations of Principal Investigators

See Section 3.0: Investigators

2.0 LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AAAAI	American Academy of Allergy, Asthma and Immunology
ACT	Asthma Control Test
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
EMA	European Medicines Agency's
FDA	Food and Drug Administration
GA	Gestational Age
GINA	The Global Initiative for Asthma
GSK	GlaxoSmithKline
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
MTB	MotherToBaby
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

3.0 INVESTIGATORS

Principal Investigator

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4.0 OTHER RESPONSIBLE PARTIES

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 conducted the study with review and input from the MAH. The OTIS Research Center received 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) assisted the OTIS Research Center in raising awareness of the study among healthcare providers who treat women with more severe asthma and was responsible for organizing and hosting the annual Scientific Advisory Committee meetings for this study.

5.0 MILESTONES

Milestone	Planned date	Actual date
Start of data collection	2016	November 3, 2016
End of data collection	2023	February 6, 2024
Registration in the EU PAS register	Jun-2016 – after Final Protocol is Approved	June 15, 2016
Final report of study results	2024	July 2024

6.0 RATIONAL 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 (Moore, 2007; Godard, 2002; Antonicelli, 2004). About two-thirds of severe asthma patients are reported to have severe eosinophilic asthma in which their symptoms are associated with too many eosinophils (a type of white blood cells) in the blood and in phlegm in the airways.

Mepolizumab is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 6 years and older, and with an eosinophilic phenotype. It is administered as a 100mg subcutaneous injection given every 4 weeks. In randomized controlled trials mepolizumab has demonstrated about a 50% reduction in asthma exacerbations during the treatment period (Haldar, 2009).

The prevalence of asthma and severe asthma in women of childbearing age, coupled with the chronic nature of treatment and the preset periodicity with which mepolizumab 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. A pregnancy exposure cohort study was undertaken to assess the safety of mepolizumab in pregnancy.

7.0 RESEARCH QUESTIONS AND OBJECTIVES

The purpose of the Mepolizumab Pregnancy Exposure Study was to monitor planned and unplanned pregnancies exposed to mepolizumab and to evaluate the possible teratogenic effect of this medication relative to the primary pregnancy outcome of major birth defects and the secondary pregnancy outcomes of preterm delivery, small for gestational age infants and spontaneous abortion or stillbirth.

8.0 RESEARCH METHODS

The research methods described below are based on the final protocol (Version 2.0, 29 January 2020; Appendix I).

8.1 STUDY DESIGN

This was a prospective, observational, exposure cohort study of pregnancy outcomes in women exposed to mepolizumab during pregnancy compared to pregnancy outcomes in women with a diagnosis of asthma who did not used mepolizumab but who had used other asthma medications during pregnancy (treated disease comparison group), and pregnancy outcomes in women not diagnosed with asthma who were not exposed to any known teratogens but may have been exposed to non-teratogenic agents (see list of known teratogens in the protocol Annex 2); (non-disease comparison group). The study was conducted by the Organization of Teratology Information Specialists (OTIS) Research Center located at the University of California San Diego. The registry relied on voluntary reporting of pregnancy and exposures by women and health care providers who contacted the North American OTIS network of teratogen information counselling services.

The study design was appropriate for the study objectives in that mothers were enrolled before the known outcome of the pregnancy, and a range of adverse pregnancy outcomes could be evaluated.

The study design included the identification of women with mepolizumab exposure in pregnancy, and two appropriate comparison groups. The treated disease group assisted with evaluation of the contribution of the underlying maternal disease to adverse pregnancy outcomes, and also provided an appropriate comparison group for the mepolizumab-exposed cohort. Maternal asthma itself has been associated with a wide variety of adverse pregnancy outcomes (Rejno, 2014; Namazy, 2013; Murphy, 2011). The non-asthmatic comparison group allowed for comparison of asthmatic to non-asthmatic women, and if the distribution of underlying disease severity was similar in both the mepolizumab and the treated disease group as possible within the current clinical environment, this could further illuminate the potential contribution of the disease (and disease-severity) to outcomes.

Women who agreed to enroll were consented orally over the telephone, and completed the initial telephone interview. Depending on the gestational timing of enrollment, a number of subsequent telephone interviews were conducted during pregnancy and after birth. Medical records for both the women and infant were obtained and abstracted for information to validate exposures and outcomes. Enrolled women were 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 1 for more information on the timing of study events).

8.2 SETTING

The study population consisted of three cohorts of pregnant women.

Participants were recruited into the three cohorts on the basis of the following inclusion/exclusion criteria:

Cohort 1: Mepolizumab Exposed

Inclusion Criteria

- Eligible subjects were currently pregnant women diagnosed with asthma who contacted the OTIS Research Center and who had been exposed to mepolizumab for any number of days, at any dose, and at any time from 8 weeks before the first day of the last menstrual period up to and including the end of pregnancy.
- Eligible subjects were currently pregnant women who agreed to the conditions and requirements of the study including the interview schedule and release of medical records.

Exclusion Criteria

- Women were not be eligible for Cohort 1 if they first contacted the OTIS Research Center after prenatal diagnosis of a major birth defect.
- Women will not be eligible for Cohort 1 if they have enrolled in the study with a previous pregnancy.

Cohort 2: Treated Disease Comparison

Inclusion Criteria

- Eligible subjects were currently pregnant women diagnosed with asthma and who were exposed to asthma medications for any number of days, at any dose, and at any time from the first day of the last menstrual period up to the date of enrolment, who contacted the OTIS Research Center but who were not exposed to mepolizumab during pregnancy or within 8 weeks prior to the first day of the last menstrual period.
- Eligible subjects were currently pregnant women who agreed to the conditions and requirements of the study including the interview schedule and release of medical records.

Exclusion Criteria

- Women who received treatment with mepolizumab but who were not eligible for Cohort 1 were not eligible for Cohort 2.
- Women were not eligible for Cohort 2 if they first came in contact with the OTIS Research Center after prenatal diagnosis of a major birth defect.
- Women were not eligible for Cohort 2 if they enrolled in the study with a previous pregnancy.

Cohort 3: Non-Asthmatic Comparison

Inclusion Criteria

- Eligible subjects were currently pregnant women who contacted the OTIS Research Center who were not exposed to any known teratogenic agents as determined by the OTIS Research Center 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, and who did not have a current self-reported diagnosis of asthma. Eligible women may potentially have been exposed to non-teratogenic agents during this time period.
- Eligible subjects were currently pregnant women who agreed to the conditions and requirements of the study including the interview schedule and release of medical records.

Exclusion Criteria

- Women who were exposed to any known teratogenic agents as determined by the OTIS Research Center 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 were not be eligible for Cohort 3.
- Women were not eligible for Cohort 3 if they had a current self-reported diagnosis of asthma.
- Women were not eligible for Cohort 3 if they were in first contact with the OTIS Research Center after prenatal diagnosis of a major birth defect.
- Women were not be eligible for Cohort 3 if they enrolled in the study with a previous pregnancy.

Other exclusions:

- Any pregnancy reported retrospectively, after the outcome was known, was not be eligible for enrollment but those that were reported, including those with adverse outcomes, were referred to the Sponsor as indicated in Section 10 of the protocol.

8.2.1 MODALITIES OF RECRUITMENT

The cohort study was conducted by investigators at the University of California Research Center for the MotherToBaby/Organization of Teratology Information Specialists (OTIS) as 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 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 provided a basis for collaborative research such as this study. Thus, individual Teratogen Information Services located throughout the U.S. and Canada served as a primary source of referrals not only for mepolizumab-exposed pregnancies but also for similarly-ascertained pregnant women with a diagnosis of asthma but not treated with mepolizumab, and similarly-ascertained pregnant women not diagnosed with asthma who have not used mepolizumab nor any known human teratogen.

Other methods of raising awareness about the study were meeting exhibits at professional practice meetings nationally, regionally and locally, direct mail to health care providers, media, social media, and website. Because treatment with mepolizumab required expertise in treating severe asthma for administration, these health care providers were a particular focus of awareness activities. With the assistance of the American Academy of Allergy, Asthma and Immunology, providers who treat women with more severe asthma were a priority target for awareness.

Women who were interested in hearing more about the study were referred to or self-referred themselves to the OTIS Research Center for more information. Referrals may have been by the woman's HCP or by the OTIS service that the woman contacted directly. Those women who were interested and met the study criteria as described in Section 9.2 were invited to enroll. Women who agreed to enroll completed the oral consent process over the telephone, and completed the initial telephone interview. Depending on the gestational timing of enrollment, subsequent telephone interviews were conducted according to the Schedule shown in Table 4 Section 8.6.3 of the protocol. Follow up interviews were conducted by telephone, and medical records for both the women and infant were obtained and abstracted for information to validate exposures and outcomes.

The study population by definition consisted of volunteers; however, they were expected to represent a wide variety of maternal age, race/ethnic background, and health status (Chambers, 2013; Chambers, 2010; Bakhireva, 2008; Chambers, 1996). The participants resided in the U.S. or Canada. By definition, the study participants were all female, as this was a pregnancy study. The age of participants was expected to be between 18 and 45; however, women under the age of 18 were able to enroll with parent/guardian consent, and women over the age of 45 were also able to enroll.

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

8.3 VARIABLES

Key variables are defined below.

8.3.1 EXPOSURE VARIABLES

Mepolizumab-exposed cohort: Exposure was defined as any dose of mepolizumab for any length of time from 8 weeks prior to the first day of the last menstrual period (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 was based upon the terminal half-life of mepolizumab of approximately 20 days (clearance of mepolizumab was based on five half-lives).
Exposure was defined as yes/no in the first trimester of pregnancy for major birth defects as the primary outcome. For this study, first trimester exposure was defined as any dose between eight weeks prior to 1st day of last menstrual period and 13 weeks after 1st day of last menstrual period. However, exposure to mepolizumab in the second (>13 weeks through 26 weeks after 1st day of last menstrual period) and third trimester (>26 weeks after 1st day of last menstrual period) was considered for those selected major birth defects that are potentially biologically plausibly related to later pregnancy exposures, e.g., craniosynostosis. For spontaneous abortion, the exposure was defined as yes/no in the first 20 weeks' of gestation, and for the other secondary outcomes, exposure was defined as yes/no anytime in pregnancy.

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

8.3.2 OUTCOME VARIABLES

- **Major Birth Defects**: a major structural defect was defined and classified using the CDC coding manual (http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf), reported by the mother and validated through the medical record. The CDC coding manual was utilized to classify defects reported through the ongoing population-based Metropolitan Atlanta Congenital Defects Program (MACDP) and was based on agreed-upon criteria by CDC investigators for major structural defects regardless of etiology. Infant medical records were abstracted and reviewed by the study research team leaders. Final validation of the classification of all major birth defects reported in the study was conducted by a VAMPSS Investigator with expertise in the diagnosis of birth defects.
- **Preterm Delivery**: preterm delivery was defined as a spontaneous or induced delivery at <37 gestational weeks, reported by the mother and validated through the medical record.
- **Small for Gestational Age (SGA) Infants**: Live born infants who were ≤10th centile on birth weight for infant sex and gestational age were considered small for gestational age. The U.S. Centers for Disease Control and Prevention (National Center for Health Statistics of NCHS) growth charts were 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.
- **Spontaneous Abortion**: Spontaneous abortion was defined as spontaneous pregnancy loss prior to 20 weeks' gestation. In this study, since women enrolled after recognition of pregnancy,

spontaneous abortions were only identified after enrollment in clinically recognized pregnancies. This outcome was reported by the mother and validated through the medical record.
- **Stillbirth**: Stillbirth was defined as a fetal death that occurs >20 weeks' gestation. This outcome was reported by the mother and validated through the medical record.

8.3.3 CONFOUNDERS AND EFFECT MODIFIERS

The potential confounders/effect modifiers listed below were described:

- 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, income
- 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 asthma medications 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
- 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, (2016) guidelines.

8.4 DATA SOURCES AND MEASUREMENTS

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

For women exposed to mepolizumab or other asthma medications, information on disease severity/symptom control from the Asthma Control Test was obtained directly from the mother at each maternal telephone interview. In addition, information on asthma-related hospitalizations and physician visits was collected at the enrollment interview and each of the subsequent maternal interviews. At the conclusion of pregnancy, regardless of the outcome, participants were interviewed about the outcome including presence or absence of birth defects, pregnancy and infant complications and infant size. At this time point the Asthma Symptom Control test questions were asked again to reflect the last four weeks of pregnancy. In addition, asthma treatment regimen at enrollment according to GINA guidelines was used to classify disease severity.

Medical Records: Mothers were asked to release medical records to the study investigators from their obstetrician or other obstetric provider, specialty care provider such as allergist/pulmonologist, deliver hospital, pediatrician, and any other health care provider involved in the pregnancy. These records were abstracted and used to validate pregnancy outcomes and when necessary to provide details regarding timing or dose of mepolizumab and other asthma medications in the absence of clear information from maternal report. Self-reported prescriptions used for GINA classification were validated with medical record information where available. Pre-defined definitions for each of the study outcomes were used for classification.

Validation of classification of major birth defects, the primary outcome, was conducted periodically and before each annual and final study reports by VAMPSS Investigators, who had the relevant expertise to review the outcomes.

Table 1. Timing of Cohort Enrollment, Interviews, Medical Records

	<20 weeks gestation	16-20 weeks gestation	32-34 weeks gestation	0-6 weeks after delivery	0-12 months after delivery
Contact / Referral	√	√	√		
Enrollment and Consent	√	√	√		
Intake Interview	√	√	√		
CCI Interview I		√			
CCI Interview II			√		
Outcome Interview				√	
Medical Record Release Forms Sent for Signature				√	
Medical Record Review					√

8.5 BIAS

The primary limitation of a cohort study utilizing volunteer subjects is potential selection bias. Internal validity was addressed by using comparably selected comparison participants. However, women who agreed to enroll in the cohort study may have represented particularly high or low risk pregnancies, limiting external validity (Johnson, 2001).

Rates of early spontaneous abortion cannot be measured in a study that enrolls women after recognition of pregnancy. For this reason, the results of this study are relevant only to late first-trimester and early second-trimester pregnancy loss.
The registry included pregnancies enrolled prior to outcome, but after a prenatal test had been performed, as long as the test did not indicate the presence of a major structural defect. This practice could have potentially biased the results by lowering the overall estimate of the prevalence of birth defects (Honein, 1999). The data analysis addressed this by stratifying subjects based on use of prenatal testing prior to enrollment.

The primary analysis of major structural birth defects was restricted to pregnancies ending in at least 1 live birth. This approach can bias the estimate of the risk for major birth defects by excluding fetal losses (spontaneous abortions, induced abortions, or fetal deaths) that may have involved major birth defects. To help address this, a secondary analysis of the primary endpoint included the number of pregnancies with known outcome in both the numerator and the denominator. However, the presence or absence of a

major birth defect in spontaneous abortions or elective terminations may not be known, thereby introducing outcome misclassification.

Misclassification bias due to poor recall is thought to be reduced in prospective study designs. In addition, each participant was interviewed at several predetermined intervals during pregnancy. Misclassification bias with respect to the infant outcomes was minimized in this study design through the use of a specialized physical examination and a standardized evaluation protocol. Another strength of the study design was the low lost-to-follow-up rate.

8.6 STUDY SIZE

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

- 200 women exposed to mepolizumab at any time 8 weeks prior to 1st day of last menstrual period and throughout pregnancy
- 300 women with asthma, unexposed to mepolizumab, aiming to represent the full spectrum of asthma severity with emphasis on severe patients
- 300 non-asthmatic controls

8.7 DATA TRANSFORMATION

Data were collected using maternal interviews, questionnaires, medical record reviews, and a pregnancy exposure diary. Detailed methodology for any data transformations are documented in the statistical analysis plan (SAP) (Annex 1, Appendix II).

8.8 STATISTICAL METHODS

8.8.1 MAIN SUMMARY MEASURES

Descriptive data for maternal characteristics were summarized with means and standard deviations for continuous variables, and counts and percentages for categorical variables. Outcomes were summarized with counts and percentages, and 95% Confidence Intervals (CI) were presented. Outcomes involving time to event (spontaneous abortion and preterm delivery) were described with left truncated rates expressed as a percentage and 95% CIs. Missing data were not counted in the percentages.

8.8.2 MAIN STATISTICAL METHODS

Detailed methodology for descriptive analyses of data collected in this study is documented in the statistical analysis plan (SAP) (Annex 1, Appendix II).

The sample size for the study was projected to be 200 participants in the mepolizumab-exposed, 300 in the disease comparison cohort and 300 in the non-diseased comparison cohort. As recruitment into the mepolizumab-exposed cohort was slower than planned, formal statistical comparisons were not appropriate. Therefore, the outcomes in each cohort were summarized descriptively. The prevalence or incidence for each outcome was presented as point estimates with their 95% CIs.

Primary Endpoint

The primary analysis for the cohort study was a description of the point estimates of the birth prevalence of major structural defects and their 95% CIs in each cohort among pregnancies ending in at least one live born infant.

In addition, the point estimates of major structural defects and their 95% CIs were also calculated in each

cohort among all pregnancies excluding those that were lost-to-follow-up. For reference, the rate of major structural defects from the most recently published MACDP data was also included.

The specific major structural birth defects reported in each cohort are listed in Annex 2, Table 12.

Secondary Outcomes

The analysis of spontaneous abortion (SAB) was complicated by left truncation in the data, i.e., women entered the study at arbitrary times in gestation. Only those women who enrolled between 0 to 20 weeks' gestation were eligible for the analysis of SAB. Since they were not followed from gestational age zero, survival analysis methods were used to handle left truncation, as well as right-censoring when a participant was lost-to-follow-up prior to 20 weeks' gestation. The left-truncated Fleming-Harrington estimate at 20.0 weeks' gestation was used to estimate the SAB rate with 95% CIs in each of the cohorts (Liang and Zeger, 1986; Diggle, 2002). Stillbirths and elective terminations were analyzed in a similar fashion.

Women who enrolled prior to 37.0 weeks of gestation and delivered a live born singleton or were lost-to-follow-up but provided at least one day of follow-up after enrollment (excluding multiple births) were eligible for the analysis of preterm delivery. These data were analyzed using the left-truncated Fleming-Harrington estimate at 37 weeks' gestation to estimate preterm delivery rates in each of the cohorts along with their 95% CIs.

Endpoints relative to small for gestational age (SGA) at birth and small for age postnatal growth at about one year of age on weight, height and head circumference, respectively, (excluding multiple births) were all binary endpoints. The analysis of each of these outcomes among singleton live births was calculated as the number and percent for the outcome with its 95% CI for each cohort group.

8.8.3 MISSING VALUES

Missing values were described in table footnotes. No imputation was performed.

8.8.4 SENSITIVITY ANALYSIS

Sensitivity analysis of the primary endpoint was conducted within each of two strata, according to whether the participant had prenatal diagnostic testing, such as level II ultrasound, amniocentesis or chorionic villus sampling, prior to enrollment in the study or not. The purpose of this was to describe potential bias introduced by prior knowledge of normal prenatal diagnostic testing results in advance of enrollment.

8.8.5 AMENDMENTS TO THE STATISTICAL ANALYSIS PLAN

A revised SAP was prepared to detail the descriptive analyses necessitated by the limited sample size.

8.9 QUALITY CONTROL

Quality control measures were in place throughout the entire period of data collection and data entry. Training and retraining of study staff was monitored per study SOP, and validation of data entry for critical study variables was conducted for 100% of study participant interactions. Data exported for CCI [redacted] final analyses for this study were checked for logical errors, and range checks are performed. All major birth defect classifications were verified by the study investigators.

Final data sets were cleaned and utilized for preparation of the analyses and study report. All analyses (coding and output) were reviewed by the lead study statistician and at least one other staff statistician. Study reports were reviewed by the Study Manager and the Investigators. All data sets and analytic files were archived indefinitely at the OTIS Research Center, and analyses can be replicated as necessary.

8.10 PROTECTION OF HUMAN SUBJECTS

The study was approved through the University of California San Diego Human Research Protections Program (Institutional Review Board or IRB). All study participants agreed to the IRB-approved oral consent form at the time of enrollment and before completing the intake interview. Each participant was 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 delivery hospital, 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 were maintained at the Research Center.

Pregnant women under the age of 18 who were eligible for the study and who wished to participate were required to have 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 were available in English or Spanish.

9.0 RESULTS

This final report is a composite of the cumulative data for women enrolled and outcome data collected between 03 November 2016 and 21 November 2022.

9.1 PARTICIPANTS

Of the 291 participants enrolled in the prospective cohort study, 23 were enrolled in the mepolizumab-exposed cohort 1, 136 in the disease unexposed cohort 2, and 132 in the non-diseased unexposed cohort 3. Characteristics of those enrolled in the prospective cohorts are described in Table 2.

Of those enrolled, 6 (26.1%) in the mepolizumab-exposed cohort were lost-to-follow-up, compared to 25 (18.4%) in the diseased unexposed cohort, and 23 (17.4%) in the non-diseased unexposed cohort who were lost-to-follow-up. Those pregnancies that were lost-to-follow-up were not included in the outcomes analyzed categorically, e.g., major birth defects. However, they could be included in analyses of the time-to-event outcomes of spontaneous abortion and preterm delivery if there was at least one day of follow-up after enrollment.

9.2 MATERNAL CHARACTERISTICS

Table 2 describes the characteristics of participants in the three cohorts with data available for each category. The mean (standard deviation [SD]) for maternal age at estimated delivery date for the mepolizumab-exposed cohort was 32.1 (5.0), compared to 32.5 (5.0) in the diseased unexposed cohort, and 32.8 (4.7) in the non-diseased unexposed cohort. Among participants in each of the cohorts, the number of participants in the mepolizumab group who identified as white (82.6%), was higher compared to participants in the diseased unexposed cohort (73.5%), and the non-diseased unexposed cohort (72.7%). Those in the mepolizumab-exposed cohort and the diseased unexposed cohort were similar in maternal ethnicity (87.0% and 85.9% were non-Hispanic, respectively) compared to 82.6% in the non-diseased unexposed cohort. In the mepolizumab-exposed cohort, 78.3% resided in the US, while 89.7% and 87.1% resided in the US in the diseased unexposed and non-diseased unexposed

cohorts, respectively. More participants numerically in the mepolizumab-exposed cohort (75.2%) and the diseased unexposed (74.5%) were overweight or obese compared to the non-diseased unexposed cohort (65.6%). For the mepolizumab-exposed cohort, the most common source of referral for participants was healthcare professional (65.2%), compared to the diseased unexposed and non-diseased unexposed participants who were most commonly self-referred via the internet (54.8% and 40.9%, respectively).

The majority of participants in the mepolizumab-exposed cohort reported having 12-15 years of education (52.2%), compared to the majority of participants in the comparison cohorts with 15 or more years of education (65.4% diseased unexposed cohort and 70.5% non-diseased unexposed cohort). Household income above $50,000 per year was lower in the mepolizumab-exposed cohort (66.7%) compared to 75.8% and 74.2% of the comparator cohorts, respectively. The majority of Hollingshead socioeconomic status classifications that accounted for both maternal and paternal education and occupations were in the middle and higher three categories in all three cohorts; 81.8% in the mepolizumab-exposed, 86.9% diseased unexposed, and 86.3% non-diseased unexposed.

In the mepolizumab-exposed cohort, 39.1% were primigravid (i.e., current pregnancy was their first), compared to 32.4% in the diseased unexposed group, and 37.9% in the non-diseased unexposed cohort. In the mepolizumab-exposed group, 39.1% had at least one previous live birth or stillbirth delivery, compared to 52.2% in the diseased unexposed group, and 48.5% in the non-diseased unexposed cohort. More participants in the mepolizumab-exposed group had a previous pregnancy ending in at least one spontaneous abortion (39.1%) compared to 31.7% of women in the diseased unexposed cohort and 25.0% in the non-diseased unexposed cohort. Across cohorts, the majority had no previous pregnancies that ended in elective termination (87.0% mepolizumab-exposed cohort, 91.2% diseased unexposed cohort, and 89.4% non-diseased unexposed cohort).

No participants in the mepolizumab-exposed cohort had a previous pregnancy that ended in a major congenital malformation, compared to 7.4% in the diseased unexposed group and 3.8% in the non-diseased unexposed comparison group. No participants in the mepolizumab-exposed group reported a previous preterm delivery, compared to 7.4% in the diseased unexposed cohort and 6.8% in the non-diseased unexposed cohort.

In the mepolizumab-exposed cohort, 69.6% of participants reported planning pregnancy, while approximately 74% reported planning pregnancy in both of the comparison groups. Two (8.7%) participants reported in-vitro fertilization in the mepolizumab-exposed cohort compared to 6.0% in the diseased unexposed comparison and 4.6% in the non-diseased unexposed groups.

Mepolizumab-exposed pregnancies tended to enroll earlier in gestation; the mean (SD) gestational age at enrollment in weeks was 15.6 (8.6) in the mepolizumab-exposed cohort, 19.8 (8.2) in the diseased unexposed cohort, and 24.0 (8.3) in the non-diseased unexposed cohort.

Average years (SD) since first diagnosis of asthma was shorter in the mepolizumab-exposed group (13.8 (9.6)) compared to the diseased unexposed cohort (18.5 (10.1). Scores on the Global Initiative for Asthma (GINA) at the first day of the last menstrual period (LMP), were higher in the mepolizumab-exposed cohort (100% scored 5) than the diseased unexposed cohort (8.8% scored 4 or 5), indicating more severe or disabling disease. The scores at 32 weeks' gestation were similar to the scores at LMP for each group.

With respect to prenatal/multivitamins or vitamins containing folic acid, a lower percentage of participants in the mepolizumab-exposed group (43.5%) began taking supplements prior to pregnancy compared to 72.1% diseased unexposed, and 56.1% non-diseased unexposed participants. This is relevant with respect to the protective effect of folic acid, as well as the potential impact of unplanned pregnancy. The percentage of participants who reported any alcohol use in pregnancy was lower in the mepolizumab-exposed group (21.7%) compared to 44.1% in the diseased unexposed comparison, and 45.5% in the non-diseased comparison. The percentage of participants who reported any tobacco use during pregnancy was 8.7% in the mepolizumab-exposed group compared to 10.3% in the diseased

unexposed cohort, and 3.8% in the non-diseased unexposed cohort. The majority of participants had a level I ultrasound prior to enrollment (91.3% mepolizumab-exposed, 89.0% diseased unexposed, and 90.9% non-diseased unexposed). Fewer than 1.0% of participants across all cohorts had a chorionic villi sampling (CVS) or amniocentesis at any time during pregnancy.

Of those in the mepolizumab-exposed cohort, none were exposed only in the 8 weeks prior to LMP or LMP to date of conception, while 74.9% were exposed in multiple trimesters, and 25.0% were exposed only in the first trimester. Exposure to systemic corticosteroids was higher in the mepolizumab-exposed cohort (47.8%) compared to the diseased unexposed group (8.8%).

The most common comorbidities in the mepolizumab-exposed cohort group were depression (21.7%), other psychiatric conditions (21.7%), and thyroid dysfunction (21.7%). Depression was the most common comorbidity reported in the diseased unexposed comparison group (27.9%). Other psychiatric conditions were reported in 14.0% in the diseased unexposed group, and thyroid dysfunction was reported in 10.3% in the diseased unexposed group, and 7.5% of participants in the non-diseased unexposed comparison group.

Table 2. Maternal Characteristics of Pregnancies in the Cohort Groups

	Mepolizumab-Exposed (N = 23)	Diseased Unexposed (N = 136)	Non-Diseased Unexposed (N = 132)
Maternal Demographics			
Maternal age (years) at estimated delivery date, categorical, n (%)			
<25 years	3 (13.0)	12 (8.8)	8 (6.1)
25-29 years	5 (21.7)	24 (17.6)	25 (18.9)
30-34 years	6 (26.1)	48 (35.3)	43 (32.6)
>34 years	9 (39.1)	52 (38.2)	56 (42.4)
Maternal Age at Estimated Due Date - Mean (Standard Deviation)	32.1 (5.0)	32.5 (5.0)	32.8 (4.7)
Maternal race[a], n (%)			
White	19 (82.6)	100 (73.5)	96 (72.7)
Black	2 (8.7)	15 (11.0)	16 (12.1)
Asian/Pacific Islander	0	9 (6.6)	10 (7.6)
Native American	0	3 (2.2)	1 (0.8)
Other	2 (8.7)	8 (5.9)	9 (6.8)
Maternal ethnicity[b], n (%)			
Non-Hispanic	20 (87.0)	116 (85.9)	109 (82.6)
Hispanic	3 (13.0)	19 (14.1)	23 (17.4)
Maternal education category, n (%)			
<12 years	0	7 (5.1)	3 (2.3)
12-15 years	12 (52.2)	40 (29.4)	36 (27.3)
>15 years	11 (47.8)	89 (65.4)	93 (70.5)
Hollingshead socioeconomic category[c], n (%)			
Low	4 (18.2)	17 (13.1)	17 (13.7)
High	18 (81.8)	113 (86.9)	107 (86.3)
Maternal Height (cm) -Mean (Standard Deviation)	161.2 (7.1)	165.1 (6.9)	163.9 (6.7)
Maternal Pre-pregnancy Body Weight (kg) - Mean (Standard Deviation)	75.2 (21.0)	74.5 (18.5)	65.6 (12.7)
Maternal pre-pregnancy body mass index (BMI)[d], n (%)			
<18.5 (underweight)	0	1 (0.7)	5 (3.8)
18.5-24.9 (normal weight)	5 (21.7)	62 (46.3)	79 (60.3)
25-29.9 (overweight)	11 (47.8)	29 (21.6)	27 (20.6)
≥30 (obese)	7 (30.4)	42 (31.3)	20 (15.3)
Gestational Age at Time of Enrollment – Weeks - Mean (Standard Deviation)	15.6 (8.6)	19.8 (8.2)	24.0 (8.3)
Gestational Age at Time of Enrollment Category – Weeks – n (%)			
≤13 weeks	11 (47.8)	30 (22.1)	15 (11.4)
13.1-19.9 weeks	6 (26.1)	40 (29.4)	21 (15.9)
≥20 weeks	6 (26.1)	66 (48.5)	96 (72.7)
Referral source[e], n (%)			
Sponsor	2 (8.7)	0	0
Health-care Professional	15 (65.2)	18 (13.3)	3 (2.3)
UC Rely	0	10 (7.4)	37 (28.0)

	Mepolizumab-Exposed (N = 23)	Diseased Unexposed (N = 136)	Non-Diseased Unexposed (N = 132)
Internet	6 (26.1)	74 (54.8)	54 (40.9)
Patient Support Group	0	2 (1.5)	0
OTIS Member Service	0	22 (16.3)	30 (22.7)
Other	0	9 (6.7)	8 (6.1)
Maternal Country of residence, n (%)			
U.S.	18 (78.3)	122 (89.7)	115 (87.1)
Canada	5 (21.7)	14 (10.3)	17 (12.9)
Family Income Category[f] – n (%)			
<$10,000	1 (4.8)	9 (6.8)	9 (7.0)
$10,000 - $49,999	6 (28.6)	23 (17.4)	24 (18.8)
≥$50,000	14 (66.7)	100 (75.8)	95 (74.2)
Year of Enrollment – n (%)			
Year 2016-2017	2 (8.7)	56 (41.2)	81 (61.4)
Year 2018-2019	6 (26.1)	67 (49.3)	51 (37.9)
Year 2020-2021	14 (60.9)	13 (9.6)	1 (0.8)
Year 2022-2024	1 (4.3)	0	0
Intended Pregnancy – n (%)	16 (69.6)	100 (73.5)	98 (74.2)
In Vitro Fertilization (IVF) – n (%)	2 (8.7)	8 (6.0)	6 (4.6)
Paternal Demographics			
Paternal age (years) at estimated delivery date, categorical[g], n (%)			
<25 years	1 (4.8)	9 (7.3)	6 (4.7)
25-29 years	4 (19.0)	16 (12.9)	18 (14.1)
30-34 years	4 (19.0)	38 (30.6)	39 (30.5)
>34 years	12 (57.1)	61 (49.2)	65 (50.8)
Paternal Age at Estimated Due Date - Mean[g] (Standard Deviation)	34.1 (5.1)	34.3 (6.1)	34.5 (5.9)
Pre-Pregnancy History			
Gravidity – Number of times ever pregnant, n (%)			
1	9 (39.1)	44 (32.4)	50 (37.9)
2-3	11 (47.8)	67 (49.3)	55 (41.7)
4-5	3 (13.0)	17 (12.5)	18 (13.6)
≥6	0	8 (5.9)	9 (6.8)
Parity – Number of previous live birth or stillbirth deliveries, n (%)			
0	14 (60.9)	65 (47.8)	68 (51.5)
1-2	8 (34.8)	62 (45.6)	52 (39.4)
3-4	1 (4.3)	7 (5.1)	10 (7.6)
≥5	0	2 (1.5)	2 (1.5)
Number of previous pregnancies ending in spontaneous abortion, n (%)			
0	14 (60.9)	93 (68.4)	99 (75.0)
1	9 (39.1)	27 (19.9)	26 (19.7)
2	0	8 (5.9)	4 (3.0)
≥3	0	8 (5.9)	3 (2.3)
Number of previous pregnancies ending in elective termination/abortion, n (%)			
0	20 (87.0)	124 (91.2)	118 (89.4)

	Mepolizumab-Exposed (N = 23)	Diseased Unexposed (N = 136)	Non-Diseased Unexposed (N = 132)
1	3 (13.0)	9 (6.6)	8 (6.1)
2	0	2 (1.5)	4 (3.0)
≥3	0	1 (0.7)	2 (1.5)
Previous pregnancies with a major congenital malformation, n (%)	0	10 (7.4)	5 (3.8)
Previous pregnancies ending in preterm delivery, n (%)	0	10 (7.4)	9 (6.8)
Maternal Disease			
Years Since Diagnosis of Primary Disease – Year – Mean (Standard Deviation)	13.8 (9.6)	18.5 (10.1)	----
Maternal Age at Diagnosis of Primary Disease – Year – Mean (Standard Deviation)	17.5 (10.0)	13.2 (9.8)	----
Global Initiative for Asthma (GINA) classification[h]			
Last Menstrual Period (LMP) or First Use of Medication after LMP			----
1	0	73 (53.7)	----
2	0	27 (19.9)	----
3	0	24 (17.6)	----
4	0	11 (8.1)	----
5	23 (100.0)	1 (0.7)	----
Unable to Classify	0	0	----
Global Initiative for Asthma (GINA) classification[h]			----
32 weeks[i]			----
1	0	33 (44.6)	----
2	0	18 (24.3)	----
3	0	13 (17.6)	----
4	0	10 (13.5)	----
5	9 (100.0)	0	----
Unable to Classify	0 (0.0)	0	----
Maternal Exposure			
Prenatal, multivitamin or folic acid supplement use and timing in pregnancy, n (%)			
Began prior to conception	10 (43.5)	98 (72.1)	74 (56.1)
Post-conception only	13 (56.5)	38 (27.9)	57 (43.2)
Have not taken at all	0	0	1 (0.8)
Any alcohol use in pregnancy, n (%)	5 (21.7)	60 (44.1)	60 (45.5)
Any tobacco use in pregnancy, n (%)	2 (8.7)	14 (10.3)	5 (3.8)
Any caffeine use in pregnancy, n (%)	21 (91.3)	120 (88.2)	104 (78.8)
Prednisone and/or Systemic Oral Corticosteroid Use in Pregnancy – n (%)	11 (47.8)	12 (8.8)	1 (0.8)
Methotrexate Use in Pregnancy - n (%)	0	1 (0.7)	0
Exposure to a Known Human Teratogen in Pregnancy – n (%)	0	4 (2.9)	0
Dose and Frequency of Mepolizumab[j]			
100 mg every 4 weeks	15 (65.2)	----	----
200 mg every 4 weeks	1 (4.3)	----	----

	Mepolizumab-Exposed (N = 23)	Diseased Unexposed (N = 136)	Non-Diseased Unexposed (N = 132)
300 mg every 4 weeks	1 (4.3)	----	----
Other	5 (21.7)	----	----
Gestational Timing of Mepolizumab Dose in Pregnancy[k,l, m]			
8 weeks prior to LMP to <LMP	0	0	0
LMP to < DOC only[n]	0	0	0
1st Trimester only	4 (25.0)	0	0
1st and 2nd Trimesters only	1 (6.2)	0	0
1st and 3rd Trimesters only	0	0	0
1st, 2nd, and 3rd Trimesters	10 (62.5)	0	0
2nd Trimester only	0	0	0
2nd and 3rd Trimesters only	1 (6.2)	0	0
3rd Trimester only	0	0	0
Prenatal Diagnostic Tests Performed Prior to Enrollment – n (%)			
Ultrasound Level 1	21 (91.3)	121 (89.0)	120 (90.9)
Ultrasound Level 2	8 (34.8)	58 (42.6)	94 (71.2)
Chorionic villus sampling (CVS)	0	1 (0.7)	0
Amniocentesis	0	1 (0.7)	0
Prenatal Diagnostic Tests Performed Anytime in Pregnancy – n (%)			
Ultrasound Level 1	22 (95.7)	133 (97.8)	127 (96.2)
Ultrasound Level 2	15 (65.2)	116 (85.3)	121 (91.7)
Chorionic villus sampling (CVS)	0	1 (0.7)	0
Amniocentesis	0	1 (0.7)	0
Maternal Comorbidity			
Ankylosing Spondylitis	1 (4.3)	0	0
Other Autoimmune Disease	0	3 (2.2)	0
Cancer	1 (4.3)	5 (3.7)	2 (1.5)
Crohn's Disease	0	4 (2.9)	0
Depression	5 (21.7)	38 (27.9)	2 (1.5)
Chronic Hypertension	0	8 (5.9)	1 (0.8)
Lupus	1 (4.3)	1 (0.7)	0
Multiple Sclerosis	0	7 (5.1)	0
Psoriasis	1 (4.3)	1 (0.7)	0
Psoriatic Arthritis	0	0	0
Psychiatric Condition	5 (21.7)	19 (14.0)	1 (0.8)
Rheumatoid Arthritis	0	5 (3.7)	0
Thyroid Dysfunction	5 (21.7)	14 (10.3)	10 (7.5)
Ulcerative Colitis	0	1 (0.7)	0
Previous Pregnancy with Preeclampsia[o]	1 (6.7)	4 (3.6)	4 (3.8)

N: Number of participants with outcome.

[a]Participants with maternal race missing- Diseased Unexposed: 1

[b]Participants with maternal ethnicity missing- Diseased Unexposed: 1

[c] Based on four-factor Hollingshead categories incorporating maternal and paternal education and occupation; highest socioeconomic status category = 1; lowest socioeconomic status category = 5. Participants with Hollingshead score missing- Mepolizumab Exposed: 1, Diseased Unexposed: 6, Non-Diseased Unexposed: 8.

[d]Participants with maternal BMI missing- Diseased Unexposed: 2, Non-Diseased Unexposed: 1.
[e]Participants with referral source missing- Diseased Unexposed: 1.
[f]Participants with income missing- Mepolizumab Exposed: 2, Diseased Unexposed: 4, Non-Diseased Unexposed: 4.
[g]Participants with IVF missing: Diseased Unexposed 2, Non-Diseased Unexposed 1
[h]Participants with paternal age missing- Mepolizumab Exposed: 2, Diseased Unexposed: 12, Non-Diseased Unexposed: 4.
[i]Global initiative for asthma (GINA) classification is based on maternal report, and confirmed by medical records. In some cases, medical records are required to classify. Possible score 1-5 with higher score indicating more severe disease.
[j]Participants with GINA classification at 32 weeks missing- Mepolizumab Exposed: 14, Diseased Unexposed: 62
[k]Participants with dose frequency missing- Mepolizumab Exposed: 1
[l]Participants with Gestational Timing of Mepolizumab missing- Mepolizumab Exposed: 7
[m]Standard definition of the 1st trimester is [0, 11] weeks post conception, of the 2nd trimester is (11, 24] weeks post conception, of the 3rd trimester is (24, 43] weeks post conception. For this table, the 1st trimester will include LMP to DOC, i.e. if a subject is exposed in both LMP to DOC and the 1st trimester, she will be in the category of 1st Trimester
[n]Last dose occurred in [LMP, DOC)
[o]Participants with preeclampsia missing- Mepolizumab Exposed: 8, Diseased Unexposed 26, Non-Diseased Unexposed 26

9.3 OUTCOME DATA

Pregnancy outcome data are presented in Table 3 of this report. The proportion of pregnancies ending in at least one live birth was lower in the mepolizumab-exposed cohort 15/23 (65.2%), compared to the diseased unexposed cohort 109/136 (80.1%), and the non-diseased unexposed cohort 108/132 (81.8%). No stillbirths were reported in the mepolizumab-exposed cohort or the diseased unexposed cohort compared to 1 (0.8%) in the non-diseased unexposed cohort. One elective termination was reported in the mepolizumab-exposed cohort (4.3%) compared to none in the diseased unexposed cohort or in the non-diseased unexposed cohort group. Losses-to-follow-up occurred in 6/23 (26.1%) in the mepolizumab-exposed cohort, compared to 25/136 (18.4%) and 23/132 (17.4%) in the two unexposed comparison cohorts, respectively.

Table 3. Pregnancy Outcome Cohort Group Analysis

	Mepolizumab-Exposed (N = 23) n/N'(%)	Diseased Unexposed (N = 136) n/N'(%)	Non-Diseased Unexposed (N = 132) n/N'(%)
Live birth	15/23 (65.2)	109/136 (80.1)	108/132 (81.8)
Twin	0/15 (0.0)	6/109 (5.5)	6/108 (5.6)
Twin with like sex	----	3/6 (50.0)	2/6 (33.3)
Sex (male)	----	1/3 (33.3)	1/2 (50.0)
Twin with non-like sex	----	2/6 (33.3)	4/6 (66.7)
Twin with only one surviving	----	1/6 (16.7)	0/6 (0.0)
Sex (male)	----	0/1 (0.0)	----
Singleton	15/15 (100.0)	103/109 (94.5)	101/108 (93.5)
Sex (male)[a]	9/15 (60.0)	58/102 (56.9)	46/101 (45.5)
Cesarean	6/15 (40.0)	36/108 (33.3)	36/108 (33.3)
Spontaneous Abortion[c,d]	1/13	2/63	0/32
Spontaneous Abortion-Twins	0/1	0/2	----
Stillbirth	0/23 (0.0)	0/136 (0.0)	1/132 (0.8)
Termination	1/23 (4.3)	0/136 (0.0)	0/132 (0.0)
Social	0/1 (0.0)	----	----
Medical	1/1 (100.0)	----	----
Lost to Follow Up	6/23 (26.1)	25/136 (18.4)	23/132 (17.4)
No Contact	6/6 (100.0)	16/25 (64.0)	17/23 (73.9)
Withdrew	0/6 (0.0)	9/25 (36.0)	6/23 (26.1)

[a]Singleton (sex): One case missing sex in the diseased unexposed group
[b]Delivery: One case missing delivery information in the diseased unexposed group
[c]Left Truncation Accounted SAB Rate in Table 5.
dSpontaneous Abortion (SAB), including ectopic, among women prospectively enrolled and exposed prior to 20 weeks' gestation and with at least one day follow up
N: Number of subjects with pregnancy outcome
n/N' (%) is either out of total N or % of the N' subcategories under the live birth, spontaneous abortion, stillbirth, termination or lost to follow-up rows

9.4 MAIN RESULTS

Major Birth Defects:

One pregnancy of 15 ending in at least one live birth in the mepolizumab-exposed cohort resulted in an infant with a major birth defect (6.7%, 95% CI 0.33, 28.73). There were 8 of 109 live births with defects (7.3%, 95% CI 3.47, 13.46) in the diseased unexposed cohort, and 8 of 108 (7.4%, 95% CI 3.50, 13.58) in the non-diseased comparison cohort. Inclusion of pregnancy losses in the numerators/ denominators, as appropriate, resulted in 2/17 infants with a major birth defect in the mepolizumab-exposed cohort (11.8%, 95% CI 2.02, 33.73) compared to 8/111 (7.2%, 95% CI 3.41, 13.23) in the diseased unexposed cohort and 8/109 (7.3%, 95% CI 3.47, 13.46), in the non-diseased comparison cohort (Table 4). The external MACDP population reference rate was 3.0% (Table 4.1).

The specific major structural birth defects identified in the mepolizumab-exposed pregnancies was one live born infant diagnosed with penoscrotal webbing, and one pregnancy electively terminated due to prenatal diagnosis of multiple malformations (Annex 2, Table 12).

Table 4. Major Birth Defects (Exposed Pregnancies Restricted to Those Exposed to Mepolizumab at any time from the 1st day of the LMP to the end of the first Trimester)

	Mepolizumab-Exposed n/N (%) 95% CI	Diseased Unexposed n/N (%) 95% CI	Non-Diseased Unexposed n/N (%) 95% CI
Number of pregnancies ending with at least one live born infant with a major birth defect	1/15 (6.7) [0.33, 28.73]	8/109 (7.3) [3.47, 13.46]	8/108 (7.4) [3.50, 13.58]
Number of all pregnancies (excluding LTFU) with major birth defects	2/17 (11.8) [2.02, 33.73]	8/111 (7.2) [3.41, 13.23]	8/109 (7.3) [3.47, 13.46]

A pregnancy with multiple outcomes is counted as one malformed outcome if any one or more infants/fetuses are malformed.

Table 4.1. Major Birth Defects Among Pregnancies Compared to Population Reference

	Mepolizumab-Exposed n/N (%) 95% CI	MACDP Reference Rate[a] (%)
Birth Prevalence of major birth defects among all pregnancies excluding LTFU	2/17 (11.8) [2.02, 33.73]	---
Birth Prevalence of major birth defects among all pregnancies, excluding LTFU and SAB	2/16 (12.5) [2.15, 35.52]	3.0

[a]MACDP (Metropolitan Atlanta Congenital Defects Program). Morbidity and Mortality Weekly Report (MMWR) January 11, 2008 / 57(01):1-5. To be included in the numerator for calculation of rate in MACDP, live born or stillborn infants with defects must have a gestational age of at least 20 weeks; electively terminated pregnancies with defects can be of any gestational age; in any live born infant, a birth defect must be identified by the child's sixth birthday.

Secondary Outcomes

Spontaneous abortion

There was one spontaneous abortion reported in the mepolizumab-exposed group, 2 in the disease unexposed group, and none in the non-diseased unexposed group. The left-truncation accounted Fleming-Harrington rates were 11.8% (95% CI 1.7%, 58.8%); 14.2% (95% CI 3.7%, 46.6%); and 0.0%, in each cohort respectively (Table 5).

Table 5. Spontaneous Abortion (SAB) among Women Prospectively Enrolled and Exposed prior to 20 Weeks' Gestation and with at Least One Day of Follow-Up

	Mepolizumab-Exposed (N = 13)	Diseased Unexposed (N = 63)	Non-Diseased Unexposed (N = 32)
Number of SAB Events [a]	1	2	0
Left Truncation Accounted SAB Rate [95% CI] [b, c, d, e]	11.8% [1.7%, 58.8%]	14.2% [3.7%, 46.6%]	----

[a]In pregnancies involving multiples (twins/triplets) with one or more of the outcomes ending in spontaneous abortion, when there are no live births, the pregnancy is counted as one spontaneous abortion event; however, when the pregnancy ends in at least one live-born infant, the pregnancy is counted as a live birth outcome.
[b]SAB rate computed using Fleming-Harrington estimate at 20 weeks' gestation, accounting for left truncation because women can enroll at various times in gestation.
[c]Fifteen LTFU cases had zero days of follow-up and were not included: 4 Mepolizumab-Exposed, 7 Diseased Unexposed, 4 Non-Diseased Unexposed.
[d]Earliest gestational age at enrollment (weeks): Mepolizumab-Exposed 5.4, Diseased Unexposed 5.4, Non-Diseased Unexposed 5.7.
N: Number of subjects enrolled and exposed prior to 20 weeks' gestation and with follow up.

Elective Abortion

There was one elective abortion in the mepolizumab-exposed cohort, none in the diseased unexposed cohort, and none in the non-diseased unexposed cohort.

Stillbirth

There were no stillbirths in the mepolizumab-exposed cohort, none in the disease-matched unexposed cohort and 1 in the non-diseased unexposed cohort.

Preterm delivery

There were no pregnancies resulting in preterm delivery among 17 ending in live born singleton infants or LTFU with at least one day of follow-up in the mepolizumab-exposed cohort. There were 8 preterm deliveries among 105 pregnancies in the diseased unexposed cohort, and 7 preterm deliveries among 96 pregnancies in the non-diseased unexposed cohort. The corresponding Fleming-Harrington rates were 0.0%, 8.1% (95% CI 4.1%, 15.5%), and 7.8% (95% CI 3.8%, 15.7%), in each cohort, respectively (Table 6).

Table 6. Preterm Delivery among Pregnancies Prospectively Enrolled (and in Mepolizumab-Exposed Cohort Also Exposed) Prior to 37 Weeks' Gestation and Ending in Live Birth or LTFU with at Least One Day of Follow-up (Multiple Pregnancies Excluded)

	Mepolizumab-Exposed (N = 17)	Diseased Unexposed (N = 105)	Non-Diseased Unexposed (N = 96)
Number of PTD (n)	0	8	7
Left Truncation Accounted PTD Rate [95% CI] [a,b,c]	----	8.1% [4.1%, 15.5%]	7.8% [3.8%, 15.7%]

[a]Computed using Fleming-Harrington estimate at 37 weeks gestation.
[b]Forty LTFU cases had zero days of follow-up and were not included: 4 Mepolizumab-Exposed, 19 Diseased Unexposed, 17 Non-Diseased Unexposed.
[c]One subject in the Diseased Unexposed Group was removed from this table, because she had a livebirth with gestational age at delivery unavailable.
N: Number of subjects enrolled and exposed prior to 37 weeks' gestation, ending in live birth singleton or LTFU with at least one day follow-up.

Small for gestational age and Small for age on postnatal growth:

By definition, approximately 10% of infants are expected to meet criteria for small for gestational age at delivery due to the normal distribution of infant size. In the mepolizumab-exposed cohort, among liveborn singletons with weight, length and head circumference data available, 2/15 (13.3%, 95% CI 2.30, 37.52) were SGA on birth weight, 1/12 (8.3%, 95% CI 0.41, 34.75) was SGA on length, and 1/6 (16.7%, 95% CI 0.84, 59.09) was SGA on birth head circumference. None of these infants were small on both weight or length and head circumference. In the diseased unexposed cohort, 10/81 (12.3%, 95% CI 6.44, 20.90) were SGA for head circumference. In the non-diseased unexposed cohort, there were no percentiles above 10% for SGA on birth weight, length or head circumference (Table 7).

At 1-year follow-up, 1/5 (20.0%, 95% CI 1.00, 66.56) infants was small on postnatal weight, and length in the mepolizumab-exposed cohort based on those for whom data were available. In both comparison groups, the proportion of small infants at about 1 year of age exceeded the 10% expected in the general population on weight, but did not on length or on head circumference (Table 8).

Table 7. Small for Gestational Age (SGA) [a] at Birth Among Live Born Infants (Multiple Pregnancies Excluded)

	Mepolizumab - Exposed (N = 15) n/N' (%) 95% CI	Diseased Unexposed (N = 103) n/N' (%) 95% CI	Non-Diseased Unexposed (N = 101) n/N' (%) 95% CI
SGA on Weight	2/15 (13.3) [2.30, 37.52]	8/101 (7.9) [3.75, 14.49]	8/100 (8.0) [3.78, 14.62]
SGA on Length	1/12 (8.3) [0.41, 34.75]	5/99 (5.1) [1.87, 10.84]	1/96 (1.0) [0.05, 5.03]
SGA on Occipitofrontal Circumference (OFC)	1/6 (16.7) [0.84, 59.09]	10/81 (12.3) [6.44, 20.90]	7/77 (9.1) [4.06, 17.15]
SGA on weight and/or length, but not OFC	0/10 (0.0) [0.00, 25.90]	2/94 (2.1) [0.36, 6.85]	3/93 (3.2) [0.80, 8.50]
SGA on weight and/or length, and OFC	0/10 (0.0) [0.00, 25.90]	2/94 (2.1) [0.36, 6.85]	2/93 (2.2) [0.36, 6.92]

[a]SGA defined as ≤10th centile for gestational age and sex
One subject in the Diseased Unexposed Group was removed from this table, because she had a livebirth with gestational age at delivery unavailable.
N: Number of singleton live born infants
N' at each category of growth measurement: Number of live born singletons for whom the specific growth measurement is available.

Table 8. Postnatal Growth at Approximately One Year – Percentile ≤10th (Multiple Pregnancies Excluded)

	Mepolizumab - Exposed (N = 15) n/N' (%) 95% CI	Diseased Unexposed (N = 103) n/N' (%) 95% CI	Non-Diseased Unexposed (N = 101) n/N' (%) 95% CI
Weight ≤10th centile[a]	1/5 (20.0) [1.00, 66.56]	11/69 (15.9) [8.68, 26.02]	12/62 (19.4) [10.93, 30.59]
Length ≤10th centile[a]	1/5 (20.0) [1.00, 66.56]	4/69 (5.8) [1.87, 13.39]	4/60 (6.7) [2.15, 15.30]
Occipitofrontal Circumference ≤10th centile[a]	0/5 (0.0) [0.00, 45.07]	0/68 (0.0) [0.00, 4.31]	3/58 (5.2) [1.33, 13.43]

[a]≤10th centile for chronological age. Age adjusted if child is less than 12 months, unadjusted if ≥12 months. Measurements are taken at 12 months of age +/- 3 months
N: Number of singleton infants who have reached one year of age
One subject in the Diseased Unexposed Group was removed from this table, because she had a livebirth with gestational age at delivery unavailable.
% = (n/N') * 100: N' at each category of growth measurement: Number of singleton infants for whom the specific percentile information is available.

9.5 OTHER ANALYSES

Additional Analyses for the Primary Outcome

There were no cases of multiple births in the mepolizumab-exposed cohort, however Table 9 shows the point estimate and 95% confidence intervals for participants in the comparison groups who had a multiple pregnancy resulting in at least one child with a major malformation.

There were 2 major birth defects in pregnancies in the mepolizumab-exposed, 6 in the diseased unexposed group, and 8 in the non-diseased unexposed cohorts where prenatal diagnostic testing prior to enrollment had occurred (Table 11 and Table 12).

Table 9. Major Birth Defects among Pregnancies with Multiple Outcomes (Exposed Pregnancies Restricted to Those Exposed to Mepolizumab at any time from the 1st day of the LMP to the end of the first Trimester)

	Mepolizumab-Exposed n/N' (%) [95% CI]	Diseased Unexposed n/N' (%) [95% CI]	Non-Diseased Unexposed n/N' (%) [95% CI]
Number of pregnancies ending with at least one live born infant with a major birth defect	----	1/6 (16.7) [0.84, 59.09]	0/7 (0.0) [0.00, 34.82]
Number of all pregnancies (excluding LTFU) with major birth defects	----	1/6 (16.7) [0.84, 59.09]	0/7 (0.0) [0.00, 34.82]

A pregnancy with multiple outcomes is counted as one malformed outcome if any one or more infants/fetuses are malformed.
N': Number of infants in a pregnancies resulting in more than one fetus. In the Mepolizumab-exposed group, the denominator is restricted to those with exposure to mepolizumab between LMP and the end of the first trimester.

Table 10. Major Birth Defects among Women Who Had Prenatal Diagnostic Testing prior to Enrollment (Exposed Pregnancies Restricted to Those Exposed to Mepolizumab at any time from the 1st day of the LMP to the end of the first Trimester) [a]

	Mepolizumab-Exposed n/N (%) [95% CI]	Diseased Unexposed n/N (%) [95% CI]	Non-Diseased Unexposed n/N (%) [95% CI]
Number of pregnancies ending with at least one live born infant with a major birth defect	1/6 (16.7) [0.84, 59.09]	6/50 (12.0) [5.01, 23.30]	8/79 (10.1) [4.82, 18.32]
Number of all pregnancies (excluding LTFU) with major birth defects	2/7 (28.6) [5.10, 66.98]	6/50 (12.0) [5.01, 23.30]	8/80 (10.0) [4.75, 18.10]

A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.
[a]Prenatal diagnostic tests include Ultrasound Level 2, Chorionic villus sampling (CVS), and Amniocentesis.
N: Number pregnancies that had prenatal testing prior to enrollment. In the Mepolizumab-exposed group, the denominator is restricted to those with exposure to mepolizumab between LMP and the end of the first trimester.

Table 11. Major Birth Defects among Women Who Did Not Have Prenatal Diagnostic Testing [a] prior to Enrollment (Exposed Pregnancies Restricted to Those Exposed to Mepolizumab at any time from the 1st day of the LMP to the end of the first Trimester)

	Mepolizumab-Exposed n/N (%) [95% CI]	Diseased Unexposed n/N (%) [95% CI]	Non-Diseased Unexposed n/N (%) [95% CI]
Number of pregnancies ending with at least one live born infant with a major birth defect	0/9 (0.0) [0.00, 28.31]	2/59 (3.4) [0.57, 10.75]	0/29 (0.0) [0.00, 9.81]
Number of all pregnancies (excluding LTFU) with major birth defects	0/10 (0.0) [0.00, 25.89]	2/61 (3.3) [0.56, 10.41]	0/29 (0.0) [0.00, 9.81]

A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.

[a]Prenatal diagnostic tests include Ultra Sound Level 2, Chorionic villus sampling (CVS), and Amniocentesis.

N: Number pregnancies that did not have prenatal testing prior to enrollment. In the Mepolizumab-exposed group, the denominator is restricted to those with exposure to mepolizumab between LMP and the end of the first trimester.

9.6 ADVERSE EVENTS/ADVERSE REACTIONS

Two study adverse events (AEs) with possible causality with exposure to mepolizumab were reported (defined per the patient population and study period specified in the protocol). One participant went to the emergency room for irregular breathing and influenza. A second participant reported migraines, which were assessed to have possible causality with exposure to mepolizumab.

Explicit attribution was not inferred by a temporal relationship between drug administration and an AE but was based on a consultant physician assessing causality, or a definite statement of causality by a healthcare provider for a study participant or a study participant linking drug administration to the AE.

10.0 DISCUSSION

Literature Review

At each of the annual Scientific Advisory Board meetings that began in 2017, any publications relevant to the Registry were provided to the Advisors and reviewed by the investigators. A brief summary of the literature is provided below.

Risks for Adverse Pregnancy Outcomes Associated with Maternal Asthma

Asthma is a common condition that has been associated with an increased risk for adverse perinatal outcomes (Kwon, 2006; Murphy, 2011; Rejno, 2014).

Murphy, (2013), published a meta-analysis on risk of congenital malformations, perinatal mortality and neonatal hospitalizations in pregnant women with asthma. Studies were included if they were published between 1975 and March 2012, cohort studies including pregnant women with and without asthma, and where at least one of the following outcomes was reported: congenital malformations, perinatal mortality, stillbirth, neonatal death, neonatal hospitalization, or specific neonatal complications. The authors found that maternal asthma compared to women without asthma was associated with an increased risk of any congenital malformation (minor or major) (relative risk [RR] 1.11, 95% confidence interval [95% CI] 1.02–1.21), but no significant risk of major malformations (RR 1.31, 95% CI 0.57–3.02) was identified, with the exception of an increased risk for cleft lip with or without cleft palate (RR 1.30, 95% CI 1.01–1.68). An association was also found with a risk for neonatal death (RR

1.49, 95% CI 1.11–2.00), and neonatal hospitalization (RR 1.50, 95% CI 1.03–2.20) in infants of mothers with asthma compared to infants of mothers without asthma. No increased risk for stillbirth (RR 1.06, 95% CI 0.9–1.25) was identified in women with asthma compared to those without asthma. Murphy concluded that there are small increased risks in women with asthma.

Murphy, (2011) conducted a meta-analysis of adverse perinatal outcomes in women with asthma. Studies were included if they were published between 1975 and March 2009, cohort studies involving a group of women with asthma, and a comparison group, and if at least one outcome of interest was included (size at birth, gestational age at delivery, and preeclampsia). Murphy reported that asthma was associated with a significantly increased risk for low birthweight when compared with women without asthma (RR 1.46, 95% CI 1.22–1.75), as well as an increased risk for small for gestational age (SGA) in women with asthma (RR 1.22, 95% CI 1.14–1.31). Maternal asthma was also associated with a significant increased risk of preterm delivery (RR 1.41, 95% CI 1.23–1.62) and preeclampsia (RR 1.54, 95% CI 1.32–1.81) compared with mothers without asthma. The authors concluded that pregnant women with asthma are at an increased risk of adverse perinatal outcomes, however the risks may be greater those with severe or uncontrolled asthma, or those experiencing exacerbations during pregnancy.

Rejno, (2014), had similar finding to Murphy, 2011, when reporting on data identified in Swedish Medical Birth Register between July 2006 and December 2009. A total of 266,045 women gave birth to 284,214 singleton infants, and of these, asthma was documented in 26,586 (9.4%) of the pregnancies. The authors found an association between asthma during pregnancy and a risk for pregnancy and infant complications. Significantly increased rates of preeclampsia (adjusted odd ratio [OR] = 1.15; 95% CI, 1.06-1.24), caesarean section (adj OR = 1.29; 95% CI, 1.23-1.34), SGA (adj OR = 1.23 95% CI: 1.13-1.33), and low birth weight infants (adj OR = 1.32 95% CI: 1.20-1.45). The authors concluded that maternal asthma is associated with a risk for pregnancy and infant complications, some that are more likely with increased asthma severity.

Wang, (2014), conducted a meta-analysis to evaluate the risk of maternal and placental complications in pregnant women with asthma. Studies were included if they were published between 1975 and March 2012, cohort studies involving a group of women with or without asthma, or a group of women with asthma stratified on medication use, and if at least one outcome of the following outcomes was included: cesarean delivery, gestational diabetes, antepartum and postpartum hemorrhage, placenta previa, placental abruption, chorioamnionitis, or premature rupture of the membranes. Women with asthma had a significantly greater risk of cesarean section delivery than women without asthma (RR =1.31, 95% CI 1.22–1.39), as well as gestational diabetes (RR=1.39, 95% CI 1.17–1.66). Women with moderate to severe asthma had a significantly increased risk of cesarean section (RR=1.19, 95% CI 1.09–1.31) and gestational diabetes (RR=1.19, 95% CI 1.06–1.33) compared to women with mild asthma. Women with asthma were at higher risk for hemorrhage (antepartum: RR= 1.25, 95% CI 1.10–1.42); postpartum: RR=1.29, 95% CI 1.18–1.41), placenta previa (RR= 1.23, 95% CI 1.07–1.40), placental abruption (RR=1.29, 95% CI 1.14–1.47) and premature rupture of membranes (RR=1.21, 95% CI 1.07–1.37) than women without asthma. Data from 6 retrospective studies did not show an increased risk for chorioamnionitis among pregnant asthmatics, however studies reporting an adjusted odds ratio did show an increased risk among women with asthma (OR=2.17, 95% CI 1.97–2.39). Wang concluded that pregnant women with asthma are at an increased risk for maternal and placental complications.

Risks for Adverse Pregnancy Outcomes Associated with Maternal Exposure to Mepolizumab

Limited information has been published regarding exposure to mepolizumab during pregnancy. Published reports are limited to case reports.

Vittorakis, 2022 published a case report of a woman with asthma, nasal polyps, as eosinophilia who became pregnant while taking mepolizumab. The woman remained on treatment throughout pregnancy and delivered a healthy live born child at 40 weeks' gestation.

Ozden and Deniz, 2021 published a report of two cases of women with severe eosinophilic asthma, who had exposure to mepolizumab in the first trimester. The first case discontinued mepolizumab at recognition of pregnancy; the mother delivered a healthy live born infant. The second case terminated the pregnancy due to lack of information regarding use of mepolizumab during pregnancy.

Summary of Findings in the OTIS Mepolizumab Pregnancy Cohort Study

Although no formal comparisons were made, maternal characteristics of those in the mepolizumab-exposed cohort exhibited a nominally higher risk profile for adverse pregnancy outcomes than either of the comparison groups on several covariates. These included lower educational attainment, lower household income, higher pre-pregnancy body mass index (BMI), slightly fewer intended pregnancies, lower proportion taking prenatal vitamins/folic acid supplements at conception, higher use of systemic steroids, and higher Global Initiative for Asthma (GINA) scores at last menstrual period (LMP) and 32 weeks' gestation. Those in the mepolizumab-exposed cohort also enrolled on average earlier in gestation than those in either of the comparison groups.

For the primary outcome of major birth defects, there was one defect reported among 15 pregnancies ending in at least one live birth (6.7%, 95% CI 0.33, 28.73) vs 8/109 (7.3%, 95% CI 3.47, 13.46) in the diseased unexposed cohort, and 8/108 (7.4%, 95% CI 3.50, 13.58) in the non-diseased unexposed comparison cohort. The reported major birth defects in the mepolizumab-exposed cohort was one live born infant with penoscrotal webbing, and one pregnancy that was electively terminated due to prenatal diagnosis of multiple malformations.
There was one spontaneous abortion reported in the mepolizumab-exposed group, with an estimated rate of 11.8% and wide CIs. There were no preterm deliveries in the mepolizumab-exposed group. There were no stillbirths reported in the mepolizumab-exposed group or the diseased unexposed group, and one reported in the non-diseased unexposed group. The proportion of live born singletons small for gestational age on weight in the mepolizumab-exposed group exceeded the expected 10% based on two events, and for SGA for head circumference based on one event. The proportion of live born singleton infants small on postnatal growth at approximately 1 year of age (weight and length) in the mepolizumab-exposed group exceeded the expected 10% but was based on one event. The proportion that was small for postnatal weight was also above the expected 10% in the comparison groups.

In summary, the rates of specific adverse pregnancy outcomes that were included in this study (e.g., major birth defects, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and postnatal growth) were based on extremely small numbers of events with very wide confidence intervals, and may not be generalizable to the broader population of mepolizumab-exposed pregnancies. However, these data do not suggest a pattern of adverse outcomes associated with mepolizumab exposure.

10.1 KEY RESULTS

Among the mepolizumab-exposed pregnancies that were enrolled into the cohort, in pregnancies ending in at least one live born infants, there was 1/15 major birth defect (relative to 8/109 in the disease unexposed cohort and 8/108 in the non-diseased unexposed cohort), 1/13 spontaneous abortion (relative to 2/63 in the diseased unexposed cohort and 0/32 in the non-diseased unexposed cohort), and no preterm deliveries (relative to 8/105 in the diseased unexposed cohort and 7/96 in the non-diseased unexposed cohort). In the mepolizumab-exposed cohort, there were 2 infants SGA on weight, 1 SGA on length, and 1 SGA on head circumference, and 1 each small for age on postnatal weight and length, all exceeding the expected proportion of 10 percent. Proportions in the comparator cohorts were above the expected 10 percent for SGA on head circumference in the diseased unexposed cohort. Proportions were above the expected 10 percent for postnatal weight in both the diseased unexposed and non-diseased unexposed cohorts. There were no stillbirths in the mepolizumab-exposed group (one in the non-diseased unexposed cohort), one elective termination for a diagnosed major birth defect in the mepolizumab-exposed group (compared to none in the comparison cohorts). Overall, the sample size

for the mepolizumab-exposed cohort was extremely small; however, based on this limited sample size, there was no pattern of major anomalies identified.

10.2 LIMITATIONS

This study had several limitations. The primary limitation was sample size in the exposed cohort. While extensive data was collected on potential confounders, the limited sample size prevented any comparative adjusted analyses to address confounding. Additionally, the study approach was prospective but not randomized. The proportion of lost-to-follow-up pregnancies was relatively high in all cohorts. The study relied on volunteers which could have led to selection bias. The primary source of data was maternal report; however, validation of outcomes reported by the study participant was performed by medical record review. Sources of bias in this study are further outlined in Section 9.5. A strength of the study was overall <5% missing values for covariates.

10.3 INTERPRETATION

Due to the small sample size of mepolizumab-exposed pregnancies in this study, the findings are limited in interpretability. There was no evidence of a pattern of major birth defects in pregnancies exposed to mepolizumab, there were no stillbirths, one spontaneous abortion, and one elective termination reported in the exposed cohort.

10.4 GENERALIZABILITY

The sample size was too limited to support generalization to mepolizumab-exposed pregnancies.

11.0 OTHER INFORMATION

None

12.0 CONCLUSION

Based on very small numbers in this prospective safety study, there was no evidence of a pattern of major structural birth defects in the mepolizumab-exposed cohort. There were no stillbirths, one spontaneous abortion, one elective termination, and no preterm deliveries. Data were limited but not suggestive of an increased risk for growth deficiency. In summary, no patterns were detected; however, the sample size was too small to draw conclusions about the safety of mepolizumab in pregnancy.

Data presented for this project are too limited to draw definitive conclusions. However, no patterns were detected.

The VAMPSS external Scientific Advisory Board reviewed the final analysis report and concurred with the conclusions of the investigators.

ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Protocol		
2	SAP		

ANNEX 2 ADDITIONAL INFORMATION

1. Major malformation listing by cohort

Table 12. Major malformation by cohort group

Cohort Group	Malformation
Mepolizumab-Exposed	1. Penoscrotal webbing 2. Multiple congenital anomalies, NOS (*TAB*)
Diseased Unexposed Comparison	1. Ventricular septal defect (VSD) 2. Atrial septal defect (ASD) 3. Congenital hydronephrosis, Vesicoureteral reflux, Patent ductus arteriosus (PDA)[a], Patent foramen ovale (PFO)[a] 4. Congenital hydronephrosis secondary to left ureteropelvic junction obstruction 5. Jejunal atresia 6. Aniridia, Kidney Caliectasis[b] 7. Profound hearing loss in left ear and progressive hearing loss in right ear, due to enlarged vestibular aqueducts (EVA) in both ears, Developmental delay[b] 8. Multiple hemangiomas
Non-Diseased Unexposed Comparison	1. Muscular ventricular septal defect (VSD) 2. Muscular Ventricular septal defect (VSD) 3. Ostium secundum defect, Supraventricular tachycardia secondary to the secundum defect[b] 4. Klippel Trenaunay Syndrome 5. Neurofibromatosis 6. Congenital chordee alone (chordee without hypospadias) 7. Pyelectasis, Hydronephrosis secondary ureteral obstruction, Global Developmental delay[b] 8. Large hemangioma, Retinoblastoma[c]

[a] Not classified as a major structural malformation based on MACDP criteria
[b] Counted as a "functional" defect per the study and not classified as a major malformation
[c] Entered as a tumor and not counted as a major malformation

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TITLE PAGE

Division: Worldwide Development

Information Type: Worldwide Epidemiology Study Protocol

Title:	The Mepolizumab Pregnancy Exposure Study: a VAMPSS post marketing surveillance study of Mepolizumab safety in pregnancy
Compound Number:	SB240563
Development Phase	IV
Effective Date:	29-JAN-2020
Subject:	Safety in pregnancy
Author(s):	PPD

PASS information

Title	The Mepolizumab Pregnancy Exposure Study: a VAMPSS post marketing surveillance study of Mepolizumab safety in pregnancy
Protocol version identifier	2.0
Date of last version of protocol	09-Nov-2017
EU PAS (ENCEPP) register number	EUPAS13772
Active substance	Mepolizumab
Medicinal product	NUCALA TM
Product reference	Mepolizumab
Procedure number	Not applicable
Marketing authorisation holder(s)	GlaxoSmithKline
Joint PASS	No
Research question and objectives	To monitor planned and unplanned pregnancies exposed to mepolizumab and to evaluate the possible teratogenic effect of this medication relative to the pregnancy outcomes of major birth defects, preterm delivery, small for gestational age infants and spontaneous abortion or stillbirth.
Countries of study	United States and Canada

Authors	PPD .

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road Brentford
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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:

Investigator Signature	Date

STUDY ADVISORY COMMITTEE

The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) 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, 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 CCI [redacted] CCI 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.

1. LIST OF ABBREVIATIONS

AAAAI	American Academy of Allergy, Asthma and Immunology
AE	Adverse Event
ACT	Asthma Control Test
AE	Adverse Event
CA	California
CDC	Centers for Disease Control and Prevention
DAP	Data Analysis Plan
GA	Gestational Age
GINA	The Global Initiative for Asthma
GSK	GlaxoSmithKline
HCP	Healthcare Professional
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IgG1	Immunoglobulin G1
IRB	Institutional Review Board
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Market Authorisation Holder
MCM	Major Congential Malformation
MTB	Mother To Baby
mg	miligrams
No	Number
OTIS	Organization of Teratology Information Services
PTB	Preterm Birth
SAE	Serious Adverse Event
SGA	Small for Gestational Age
SMP	Safety Management Plan
SOP	Standard Operating Procedure

UK	United Kingdom
US	United States
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NUCALA

Trademarks not owned by the GlaxoSmithKline group of companies
SAS
Xolair

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

Global Regulatory Affairs Lead
Respiratory Therapeutic Group
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 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 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 counselling 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.

The American Academy of Allergy, Asthma and Immunology (AAAAI) will assit the OTIS Research Centre in raising awareness of the study among healthcare providers who treat women with more severe asthma.

Principal Investigator:

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3. ABSTRACT

Rational 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 do not adequately respond to current standard therapy. Mepolizumab (NUCALA™) is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype, and is given as 100 mg by subcutaneous injection every four weeks. Package labelling 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, mepolizumab will be knowingly utilized by pregnant women when they and their doctor believe the risk benefit favors its use. Also, given the long half-life, inadvertent exposure in pregnancy is likely, even upon immediate cessation of treatment once pregnancy is suspected or confirmed. We therefore propose a pregnancy exposure cohort study to assess the safety of mepolizumab in pregnancy. Information regarding the safety of mepolizumab in human pregnancy is essential from a public health perspective to help inform clinical practice.

Research Objectives and Study Design

The objectives of the study are to assess the risk or safety of mepolizumab exposure in pregnancy with respect to major birth defects, spontaneous abortion, stillbirth, preterm delivery, and small for gestational age infants. This is a prospective, observational, exposure cohort study of pregnancy outcomes in women exposed to mepolizumab during pregnancy compared to pregnancy outcomes in women with a diagnosis of asthma who have not used mepolizumab during pregnancy but have used other anti-asthmatic medications (treated disease comparison group), and pregnancy outcomes in women not diagnosed with asthma (non-disease comparison group).

Population

The study population consists of three cohorts: 1) a mepolizumab-exposed cohort with exposure to at least one dose of the drug from 8 weeks prior to the first day of the last menstrual period to the end of pregnancy; 2) a disease cohort with treated asthma who have not been exposed to mepolizumab within 8 weeks prior to the first day of the last menstrual period or throughout pregnancy; 3) a non-asthmatic cohort who have no current diagnosis of asthma and have not been exposed to any known human teratogen but may have potentially been exposed to non-teratogenic agents.

Variables

Exposure will be defined as mepolizumab treatment by maternal report and verified by medical record review. Outcome variables include major birth defects, spontaneous abortion, stillbirth, preterm delivery, and small for gestational 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, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, medication, vaccine and vitamin/mineral exposures, prenatal tests, and measures of disease severity and symptom control.

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.

Study Size and Timing

The target sample size for the study is 200 women in the mepolizumab-exposed cohort; 300 women in the treated disease cohort; and 300 women in the non-asthmatic cohort. Upon initiation of recruitment, the study is expected to continue for 6.5 years.

Data Analysis

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 mepolizumab-exposed cohort and the treated disease cohort. Where numbers permit, multivariable analyses will be conducted to determine the relationship of mepolizumab with the following primary outcomes: major birth defects, and secondary outcomes; small for gestational age, preterm delivery, spontaneous abortion and stillbirth as numbers permit.

4. AMENDMENTS AND UPDATES

GlaxoSmithKline Document Number	Date	Version
2016N282524_00	2016-MAY-12	Original
2016N282524_01	2017-NOV-09	Amendment No. 1
The purpose of the amendment is to include specific Adverse Event (AE) definition wording mandated by Health Canada, the Canadian regulatory authority. Text has been updated to state that the Final Report will include safety data related to any GSK product. Text to cover the referral of other ineligible mepolizumab-exposed pregnancies to the Sponsor has also been included. Data collection forms omitted in error from the original protocol have been included in Annex 2. Text has also been updated to reflect descriptive comparisons will be made to the Metropolitan Birth Defects Monitoring Program.		
2016N282524_02	2020-JAN-29	Amendment No. 2
The purpose of the amendment is to remove the specific data collection forms listed in Annex 2 as these have been updated and therefore are not accurately represented. Removing the data collection forms from the protocol will prevent the need for future protocol amendments if the data collections forms are updated again. There has also been a change to the Marketing Authorisation Holder contact name and contact details and this has been updated. There have also been a number of grammatical and typographical errors that have been corrected throughout the document.		

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	09-NOV-17	9	The following wording has been added: • 'An AE can therefore be any unfavourable and unintended sign (including an abnormal	The primary purpose of the amendment is to include specific Adverse Event (AE) definition wording mandated by Health Canada, the Canadian regulatory authority.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event), and adverse events associated with circumstances of Overdose whether accidental or intentional, Medication Errors, Abuse or effects of drug withdrawal, or Misuse.'	
1	09-NOV-17	9	The following wording	The text was updated to cover the referral of

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			has been added: • Other ineligible mepolizumab-exposed pregnancies will also be referred to the Sponsor.'	other ineligible mepolizumab-exposed pregnancies to the Sponsor.
1	09-NOV-17	9	The following wording has been added: 'The final study report will additionally include all adverse events that have been explicitly attributed to any known GSK product reported to the Sponsor	The text was updated to state that the Final Report will include safety data related to any GSK product.
1	09-NOV-17	7.7.1	The following wording has been added: A tertiary objective of the study is to descriptively compare the rate of major birth defects in the mepolizumab-exposed pregnancies, and control groups to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance	An additional analysis has been added to reflect OTIS standard practice of comparisons to CDC MACDP.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			program (Centers for Disease Control and Prevention, 1998).	
1	09-NOV-17	Appendix 2	The following questionnaires have been added: • MTB Pregnancy Studies: Intake-Demographics & Medical Hx, Version 12, 27January 2015 • MTB Pregnancy Studies: Exposure Interview Sheets, Version 12, 29January 2016 • Outcome – Delivery & Birth Information, revised 9/12/2011	Data collection forms omitted in error have been included in Annex 2.
2	29-JAN-20	Annex 2	The data collection forms have all been removed	Data collection forms have since been updated
2	29-JAN-20	Annex 2	The known list of Teratogens has been updated	This list has been updated to contain new teratogens including Zika.
2	29-JAN-20	Marketing Authorisation	The marketing authorisation holder	Change in marketing authorisation holder contact.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
		Holders	contact has been updated	
2	29-JAN-20	Milestones	An addition column of "Actual Date" has been added	To be transparent about the timelines of the study.
2	29-JAN-20	Sponsor contact address	The UK address has been updated.	Following change of sponsor contact address.
2	29-JAN-20	Sponsor SAE contact information	The fax number has been removed.	Fax is no longer used by the GSK Case Management group.

5. MILESTONES

Milestone	Planned date	Actual Date
Start of data collection	2016	November 3rd 2016
End of data collection	2023	
CCI [redacted]		
Registration in the EU PAS register	Jun-2016 – after Final Protocol is Approved	June 15th 2016
Final report of study results	2024	

6. RATIONAL AND BACKGROUND

6.1. 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 (Moore 2007; Godard 2002; Antonicelli 2004). About two-thirds of severe asthma patients are reported to have severe eosinophilic asthma in which their symptoms are associated with too many eosinophils (a type of white blood cells) in the blood and in phlegm in the airways.

Mepolizumab is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. It is administered as a 100mg subcutaneous injection given every 4 weeks. In randomized controlled trials mepolizumab has demonstrated about a 50% reduction in asthma exacerbations during the treatment period (Haldar 2009).

The prevalence of asthma and severe asthma in women of child bearing age, coupled with the chronic nature of treatment and the preset periodicity with which mepolizumab 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 mepoluzimab in pregnancy.

6.2. Rationale

Information regarding the safety of mepolizumab in human pregnancy is essential from a public health perspective as inadvertent pregnancy exposure to mepolizumab 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 Mepolizumab Pregnancy Exposure Study is to monitor planned and unplanned pregnancies exposed to mepolizumab and to evaluate the possible teratogenic effect of this medication relative to the primary pregnancy outcome of major birth defects and the secondary pregnancy outcomes of preterm delivery, small for gestational age infants and spontaneous abortion or stillbirth.

8. RESEARCH METHODS

8.1. Study Design

This is a prospective, observational, exposure cohort study of pregnancy outcomes in women exposed to mepolizumab during pregnancy compared to pregnancy outcomes in women with a diagnosis of asthma who have not used mepolizumab but have used other asthma medications during pregnancy (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 (see list of known teratogens in Annex 2); (non-disease 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 counselling services.

The study design is appropriate for the study objectives in that mothers are enrolled before the known outcome of the pregnancy, 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 mepolizumab exposure in pregnancy, and two appropriate comparison groups. The treated disease group assists with evaluation of the contribution of the underlying maternal disease to adverse pregnancy outcome, and also provides an appropriate comparison group for the mepolizumab-exposed cohort. This is essential, in that maternal asthma itself has been associated with a wide variety of adverse pregnancy outcomes (Rejnö, 2014; Namazy, 2013; Murphy, 2011). The non-asthmatic comparison group allows for comparison of asthmatic to non-asthmatic women, and if the distribution of underlying disease severity is similar in both the mepolizumab and the treated disease group as possible within the current clinical environment,, 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. 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. 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 5, Section 8.6.3 for more information on the timing of study events)

8.2. Study Population and Setting

The study population consists of three cohorts of pregnant women (See Section 8.5 for sample size).

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

Cohort 1: Mepolizumab Exposed

Inclusion Criteria

- Eligible subjects will be currently pregnant women diagnosed with asthma who contact the OTIS Research Center and who have been exposed to mepolizumab for any number of days, at any dose, and at anytime from 8 weeks before the first day of the last menstrual period 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 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 prenatal diagnosis of a major birth defect, although data will be collected on these retrospective reports and descriptive information will be included in annual and final study reports.
- Women will not be eligible for Cohort 1 if they have enrolled in the study with a previous pregnancy.

Cohort 2: Treated Disease Comparison

Inclusion Criteria

- Eligible subjects will be currently pregnant women diagnosed with asthma and who are exposed to asthma medications for any number of days, at any dose, and at anytime from the first day of the last

menstrual period up to the date of enrolment, who contact the OTIS Research Center but who were not exposed to mepolizumab during pregnancy or within 8 weeks prior to the first day of the last menstrual period.

- Eligible subjects 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 received treatment with mepolizumab but who are not eligble for Cohort 1 will not be eligble for Cohort 2.
- 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 birth defect.
- Women will not be eligible for Cohort 2 who have enrolled in the study with a previous pregnancy.

Cohort 3: Non-Asthmatic Comparison

Inclusion Criteria

- Eligible subjects will be currently pregnant women who contact the OTIS Research Center who were not exposed to any known teratogenic agents as determined by the OTIS Research Center (list in Annex 2) 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, and who do not have a current self-reported diagnosis of asthma. Eligible women may potentially have been exposed to non-teratogenic agents during this time period.
- Eligible subjects 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 been exposed to any known teratogenic agents as

determined by the OTIS Research Center (list in Annex 2) 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 will not be eligible for Cohort 3.

- Women will not be eligible for Cohort 3 if they have a current self-reported diagnosis of asthma.
- Women will not be eligible for Cohort 3 if they come in contact with the OTIS Research Center after prenatal diagnosis of a major birth defect.
- Women will not be eligible for Cohort 3 if they have enrolled in the study with a previous pregnancy.

Other exclusions:

- Any pregnancy reported retrospectively, after the outcome is known, will not be eligible for enrollment but those that are reported, including those with adverse outcomes, will be referred to the Sponsor as indicated in Section 10.

The cohort study will be conducted by investigators at the University of California Research Center for the MotherToBaby/Organization of Teratology Information Specialists (OTIS) as 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 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 mepolizumab-exposed pregnancies but also for similarly-ascertained pregnant women with a diagnosis of asthma but not treated with

mepolizumab, and similarly-ascertained pregnant women not diagnosed with asthma who have not used mepolizumab nor any known human teratogen.

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. Because treatment with mepolizumb will require expertise in treating severe asthma for administration, these health care providers will be a particular focus of awareness activities. With the assistance of the American Academy of Allergy, Asthma and Immunology, providers who treat women with more severe asthma will be a priority target for awareness.

Women who are interested in hearing more about the study will be referred to or will self-refer themselves to the OTIS Research Center for more information. Referrals may be by the woman's healthcare professional (HCP) or by the OTIS service that the woman contacts directly. Those women who are interested and meet the study criteria as described in Section 8.1 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 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 (Chambers, 2013; Chambers, 2010; Bakhireva, 2008; Chambers, 1996). 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; however, women under the age of 18 may enroll with parent/guardian consent, and women over the age of 45 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 subject.

Table 1 Recruitment Timetable

	Year 1	Year 2	Year 3	Year 4	Year 5
Cohort 1 Mepolizumab 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

8.3. Variables

8.3.1. Exposure definitions

Mepolizumab-exposed cohort: Exposure is defined as any dose of mepolizumab for any length of time from 8 weeks prior to the first day of the last menstrual period (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 mepolizumab of approximately 20 days (clearance of mepolizumab is based on five half-lives).

Exposure is defined as yes/no in the first trimester of pregnancy for major birth defects as the primary outcome. For this study, first trimester exposure is defined as any dose between eight weeks prior to 1st day of last menstrual period and 13 weeks after 1st day of last menstrual period. However, exposure to mepolizumab in the second (>13 weeks through 26 weeks after 1st day of last menstrual period) and third trimester (>26 weeks after 1st day of last menstrual period) 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, the 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 the first day of last menstrual period 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.

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

8.3.2. Outcome definitions

Major Birth Defects: a major structural defect is defined and classified using the CDC coding manual (http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf), 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 MACDP and is based on agreed-upon criteria by CDC investigators for major structural defects regardless of etiology. Infant medical records are abstracted and reviewed by the study research team leaders. Final validation of the classification of all major birth defects reported in the study will be conducted by a VAMPSS 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 8.3.1 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 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 the Britton growth charts will be used for preterm infants (Britton, 1993). The outcome of birthweight is reported by the mother and validated through the medical record.

Spontaneous Abortion: Spontaneous abortion is defined as spontaneous pregnancy loss prior to 20 weeks' gestation. In this study, since women enrol 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.

8.3.3. 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 a birth defects
- 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
- 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 (ACT) 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 The Global Initative for Asthma (GINA) (2016) guidelines.

Methods for identifying and controlling for these confounders and/or effect modifiers are described in Section 8.7.1. The Data Analysis Plan (DAP) 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 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 mepolizumab, taken anytime in pregnancy as well as data on a wide variety of confounders (See Section 8.3.3).

For women exposed to mepolizumab or other asthma medications, information on disease severity/symptom control from the ACT 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 Symptom Control test questions are asked again to reflect the last four weeks of pregnancy. In addition, asthma treatment regimen at enrollment 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 any other health care provider involved in the pregnancy. These records are abstracted and used to validate

pregnancy outcomes and when necessary to provide details regarding timing or dose of mepolizumab 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 classification of major birth defects, the primary outcome, is conducted periodically and before each annual and final study reports by VAMPSS Investigators, who have the relevant expertise to review the outcomes.

Table 2 Variables collected per cohort

Variable	Cohort 1 Mepolizumab-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]			
Pregnancy validation	√	√	√
Pregnancy outcome validation	√	√	√
Exposure timing validation[1]	√	√	√
Dose validation[1]	√	√	√

Variable	Cohort 1 Mepolizumab-exposed	Cohort 2 Asthmatic comparison	Cohort 3 Non-Asthmatic comparison
Self-reported prescription validation[1]	√	√	√
Major birth defects[3]	√	√	√

[1]For cohort 1& 2 primarily asthma medication 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

8.5. Study size

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

- 200 women exposed to mepolizumab at any time 8 weeks prior to 1st day of last menstrual period and throughout pregnancy
- 300 women with asthma, unexposed to mepolizumab, aiming to represent the full spectrum of asthma severity with emphasis on severe patients
- 300 non-asthmatic controls

Table 3 Risk and safety estimates for mepolizumab-exposed pregnancies relative to the primary comparison group for selected outcomes available from the cohort arm (OTIS) after 4 years of enrollment and collection of outcomes at birth; all estimates use an α-level of 0.05.*

Outcome	**No. Exposed N = 200**	**No. Unexposed Asthmatic N = 300**	**Risk****	**Safety*****
All major birth defects	180	270	3.0	2.8
Preterm birth	180	270	2.2	2.0
SGA infant	180	270	1.9	1.8

*Sample size for all outcomes shown in the table based on 90% of enrolled pregnancies ending in live birth with completed outcome; sample size for all birth defects based on prevalence of 3% in the asthmatic comparison group; sample size for preterm birth based on prevalence of 7% in the asthmatic comparison group (Bakhireva, 2008); sample size for small for gestational age infants (SGA) based on prevalence of 10% in the asthmatic comparison group. Power calculations performed in OpenEpi software.
** Minimum RR detectable with 80% power.
***Upper 95 % confidence bound for RR=1.

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

It is expected, based on experience with the EXPECT registry for omalizumab that virtually all mepolizumab-exposed participants will have exposure sometime in the first trimester and will typically enroll in the study upon recognition of pregnancy making the entire cohort analysable for the primary outcome and all secondary outcomes. It is possible that some participants in all three cohorts will enroll after 20 weeks' gestation and therefore will not be included in the analysis of spontaneous abortion.

8.6. Data management

Maternal interviews are conducted at enrolment 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 semistructured 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), paediatrician (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 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 of patient files and subject signed consent forms will be kept in locked file rooms and/or locked cabinets under the supervision of the study investigators.

8.6.1. Data handling conventions

Major birth defects are classified using the CDC coding manual (http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf) by the Study Manager. All defect classifications are reviewed by co-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 small for gestational age 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.

Table 4 Denominators by Outcome

Outcome	Denominator
Major Birth Defects Among Live Births	Pregnancies ending in live birth; with exposure in 1st trimester for mepolizumab cohort, and other comparison groups at least one malformed infant in an individual pregnancy is considered one malformed outcome
Major Birth Defects Among All Pregnancies	Pregnancies with any outcome excluding those lost-to-follow-up; with exposure in 1st trimester for mepolizumab cohort, and other comparison groups; at least one malformed foetuses/infants in an individual pregnancy is considered one malformed outcome
Spontaneous Abortion	Pregnancies enrolled in the study prior to 20 weeks' gestation with at least 1 follow-up data collection point after enrollment date. Exposure can occur any time in pregnancy prior to event.
Preterm Delivery	Pregnancies enrolled prior to 37 weeks gestation and ending in at least one live born infant; excluding twins or higher order multiples due to inherent higher risk of preterm birth in multiples. Exposure can occur any time in pregnancy prior to 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 event.
Still Birth	All pregnancies, excluding lost-to-follow-up. Exposure can occur any time in pregnancy prior to event.

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 an 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%. 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 DAP.

8.6.2. Resourcing needs

Not applicable.

8.6.3. Timings of Assessment during follow-up

Table 5 Timing of Cohort Enrollment, Interviews, Medical Records

	<20 weeks gestation	16-20 weeks gestation*	32-34 weeks gestation	0-6 weeks after delivery	0-12 months after delivery
Contact / Referral	√	√	√		
Enrollment and Consent	√	√	√		
Intake Interview	√	√	√		
CCI Interview I		√			
CCI Interview II			√		
Outcome Interview				√	
Medical Record Release Forms Sent for Signature				√	
Medical Record Review					√

8.7. Data analysis

8.7.1. Essential analysis

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

Primary Endpoint: The primary endpoint will be major structural defects among live born infants. The primary comparison will be between the first-trimester mepolizumab-exposed group and the treated disease cohort.

Secondary comparisons for major birth defects will be conducted with the denominator including all pregnancies ending in live birth, spontaneous abortion, stillbirth or elective termination, excluding lost-to-follow-up, comparing first-trimester mepolizumab-exposed to the treated disease cohort.

Additional secondary comparisons will be made between the first-trimester mepolizumab-exposed group and the treated asthma and non-asthmatic cohort. A tertiary objective of the study is to descriptively compare the rate of major birth defects in the mepolizumab-exposed pregnancies, and control groups to external data from the CDC MACDP, a population-based birth defects surveillance program (Centers for Disease Control and Prevention, 1998).

Secondary Endpoints:
Preterm Delivery: After exclusion of twins or higher order multiples, the rate of pregnancies ending in live birth <37 weeks' gestation will be compared between the mepolizumab group enrolled and exposed anytime in pregnancy prior to 37 weeks' gestation and the treated disease and non-asthmatic cohorts enrolled prior to 37 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 $\leq 10^{th}$ centile of birth

weight for gestational age and sex will be compared between the mepolizumab-exposed group and the treated disease and non-asthmatic cohorts.

Spontaneous Abortion: For those women in all three cohorts who enrolled in the study prior to 20 weeks' gestation, the rate of spontaneous abortion accounting for left truncation will be compared between those in the mepolizumab group enrolled and exposed any time in pregnancy prior to 20 weeks' gestation and the treated disease and non-asthmatic cohorts.

Stillbirth: The rate of pregnancies ending in stillbirth will be compared between those in the mepolizumab-exposed group and the treated disease and non-asthmatic cohorts.

Statistical methods: Descriptive tables will be prepared for characteristics of each of the cohorts in CCI CCI final report displaying means and standard deviations, or proportions and percentages.

For the primary endpoint of major structural defects and for the secondary endpoint of small for gestational age infants, crude comparisons will be made using exact methods to develop relative risk estimates and their 95% 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 rates and 95% confidence intervals, where numbers permit, will be conducted for major birth defects and small for gestational age infants using logistic regression. Adjusted analyses producing rates and 95% confidence intervals, for preterm delivery, spontaneous abortion and stillbirth, where numbers permit, will be conducted using Cox Proportional Hazards. 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 mepolizumab 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

8.7.2. Exploratory analysis

Exploratory analyses addressing potential effect modifiers such as ACT measures of disease symptom control, and measures of asthma exacerbation will be addressed. In addition, subanalyses based on length and gestational timing as well as dose of exposure to mepolizumab will be performed. Additionally, stratified analyses based on prenatal diagnosis 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 birth defects, but including women who have already had a normal result or prenatal diagnosis for major birth defects prior to enrollment. Therefore, the planned stratified analysis will compare the birth prevalence of major birth defects among the subset of women enrolled in the cohorts *prior to* prenatal diagnostic testing for fetal structural anomalies, to the birth prevalence of major birth defects among the subset of women enrolled in the cohorts *after* prenatal diagnostic testing for fetal structural anomalies. Subanalyses excluding chromosomal or known genetic anomalies (based on specific defects categorized by expert based on known genetic etiology) will also be conducted.

8.7.3. General considerations for data analyses

The general approach to controlling for confounding is to evaluate each relevant confounder for the specific outcome to determine if inclusion of the confounder in a model containing exposure to mepolizumab changes the estimate of the effect of exposure by 10% or more. The confounders will be assessed univariately and those confounders that are identified are incorporated into multivariate analyses as described in the statistical analysis Section 8.7.1. Further details will be contained in the DAP. Control for confounding by indication is addressed by comparison to the treated disease group. However, as described in exploratory analyses in Section 8.7.2, attention to measures of disease symptom control and underlying severity will also be addressed by subgroup and stratified analysis.

8.8. Quality control and Quality Assurance

As noted in Section 8.6, 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 SOP, and validation of data entry for critical study variables is conducted for 100% of study participant interactions. Data exported for CCI final analyses for this study are checked for logical errors, and range checks are performed. All major birth defect classifications are verified by the study investigators.

Data are reviewed on an CCI basis by the VAMPSS external advisory committee. 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 CCI 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 mepolizumab 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 timing of exposure will be in the mepolizumab-exposed cohort. In the EXPECT registry for omalizumab, pregnancy exposures were predominately limited to the first trimester (Namazy, 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 four to six 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 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 enrolment, spontaneous abortion rates in late first trimester and early second trimester will be analyzable.

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 mepolizumab-exposed pregnancies as well as appropriate comparison group pregnancies, the OTIS research groups' track record of excellent subject retention (<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.

8.9.1. Study closure/uninterpretability of results

In consultation with the 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 mepolizumab 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 mepolizumab to determine if uptake among women of reproductive age is consistent with enrollment rates in the cohort study. One of the sources of these data is the database arm of VAMPSS which represents a large population-based source of information on pregnancy exposures. Enrollment will also be reviewed with respect to key awareness activities.
- If the Sponsor discontinues manufacturing mepolizumab 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.

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. 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.

This study adopts the following International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event), and adverse events associated with circumstances of Overdose whether accidental or intentional, Medication Errors, Abuse or effects of drug withdrawal, or Misuse.

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 hospitalisation but may jeopardise 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 hospitalisation; or development of drug dependency or drug abuse.

The purpose of the Mepolizumab Pregnancy Exposure Study is to monitor planned and unplanned pregnancies exposed to mepolizumab and to evaluate the possible teratogenic effect of this medication. For mepolizumab exposed pregnancies pre-defined specific pregnancy outcomes that are classified as serious adverse events (SAE's) will be identified and reported. These selected SAEs include Major Congenital Malformation (MCM), spontaneous abortion, still birth and neonatal death. These events will be reported to the sponsor's safety department within 24 hours.

Additionally, for mepolizumab exposed pregnancies, all other adverse events, which are ascertained as part of the routine study data collection, will be abstracted from maternal interviews (and/or from available medical records) by dedicated and trained study staff. Each of the events will be assessed for causal relationship to mepolizumab exposure by a consulting physician with expertise in asthma and allergy treatment of women of reproductive age. This assessment of events will be performed on a monthly basis by the consulting physician. Only those adverse events attributed by the consulting physician to mepolizumab will be reported to the sponsor's safety department within 24 hours.

Any pregnancies in subjects exposed to mepolizumab reported to the OTIS Research Centre retrospectively, after the outcome is known, will not be enrolled and will be referred to the Sponsor. Other ineligible mepolizumab-exposed pregnancies will also be referred to the Sponsor.

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 CCI final study reports will include the serious adverse events that are the study endpoints as part of the hypotheses being tested, and a summary of all mepolizumab attributed adverse events. The final study report will additionally include

all adverse events that have been explicitly attributed to any known GSK product reported to the Sponsor.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

Healthcare providers treating women with asthma and regulatory authorities.

11.2. Study reporting and publications

Key design elements of this study will be posted in publicly accessible databases. Furthermore, key results of this study will be posted in publicly accessible databases within the required time-frame from completion of the data collection where applicable.

CCI [redacted] will be prepared on study progress annually. Upon closure of the study, a final report will be generated by the VAMPSS study investigators which will be submitted by GSK to the relevant regulatory authorities. The final report will also be available to HCPs.

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 VAMPSS investigators and in accordance with the current guidelines for STrengthening the Reporting of OBservational studies in Epidemiology (von Elm, 2008). VAMPSS 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.

12. REFERENCES

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13. APPENDICES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Tables and Figures

Core table shells and figures will be included in the DAP

Stand-Alone Documents

None

ANNEX 2. Additional Information

Disqualifiers for MTB NON-DISEASED CONTROLS

Known Human Teratogens – Disqualifiers for non-diseased controls for ALL MTB Studies:

If CA resident, refer to MTB-CA (exposed)

*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).*

Go to http://www.clinicalpharmacology-ip.com/Default.aspx to look at med category & look up generic name.

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	*OK to enroll in Catchall*
Propylthiouracil (PTU)	
Radiation, High Dose	≥ 5 rads to the uterus
Rubella	
Thalidomide	
Toxoplasmosis	
Varicella	Primary case of chicken pox
Warfarin (Coumadin, Jantoven) derivatives	
Zika, Confirmed	Positive test result

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: 200870

Nucala™ (Mepolizumab) Pregnancy Exposure Registry: A VAMPSS post marketing surveillance study of Mepolizumab safety in pregnancy

COMPOUND: Nucala™/Mepolizumab/SB240563

STUDY BIOSTATISTICIAN: Prof. PPD , PPD

DATE OF ISSUE: 11 May 2023

VERSION: 1.0

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AAAAI	American Academy of Allergy, Asthma and Immunology
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
GINA	The Global Initiative for Asthma
IVF	In Vitro Fertilization
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
M-CHAT-R	Modified Checklist for Autism in Toddlers
NCHS	National Center for Health Statistics
OTIS	Organization of Teratology Information Specialists
PS	Propensity Score
RR	Relative Risk
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGA	Small for Gestational Age
US	United States
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System

1. OVERVIEW AND STUDY PLAN

This statistical analysis plan (SAP) provides a comprehensive and detailed description of statistical approaches and techniques to analyze the data for the Nucala™ (Mepolizumab) Pregnancy Exposure Registry. This study will be conducted by the Organization of Teratology Information Specialists (OTIS), which 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).

1.1 Study design

This is a U.S. and Canada based prospective, observational, exposure cohort-matched study of pregnancy outcomes in women exposed to Nucala™ from 8 weeks prior to the first day of the last menstrual period (LMP) to the end of pregnancy. The outcomes in women with asthma exposed to Nucala™ (Cohort 1) will be compared to those observed in 2 comparison groups: a diseased cohort with treated asthma who have not been exposed to Nucala™ within 8 weeks prior to the first day of LMP (Cohort 2), and another comparison group of non-asthmatic cohort who have no current diagnosis of asthma and have not been exposed to any known human teratogens (Cohort 3). Each subject will be followed from enrollment through the end of pregnancy, and those pregnancies ending in a live born infant will be followed through a 1-year period. The overall study duration is planned for approximately 8 years with 5 years of active recruitment.

1.2 Study Objectives

1.2.1 Primary objective

To evaluate the relative risk of major structural birth defects (as defined by the Metropolitan Atlanta Congenital Defects Program (MACDP), specifically a pattern of anomalies, up to one year of age, in Nucala™-exposed pregnancies compared to the primary comparison group of disease-matched unexposed pregnancies.

1.2.2 Secondary objectives

To evaluate the risk for Nucala™ exposure relative to the secondary comparison group of non-diseased unexposed pregnant women, and the effect of exposure on other adverse pregnancy outcomes and infants outcomes including the following:

Pregnancy Outcomes:

- spontaneous abortion (SAB),
- stillbirth,
- premature delivery.

Infant Outcomes:

- small for gestational age (SGA)

1.3 Analysis population(s)

This study consists of 3 cohorts of pregnant women recruited from the U.S. and Canada, who agree to enroll at any time during pregnancy. The exposed group (Cohort 1) consists of pregnant women with asthma who have been exposed to Nucala™ for any number of days, at any dose, and at any time from 8 weeks prior to the first day of LMP up to and including the end of pregnancy.

The treated disease comparison group (Cohort 2) consists of pregnant women diagnosed with asthma, who are exposed to asthma medications for any number of days, at any dose, and at anytime from the first day of the LMP up to the date of enrollment, but not exposed to Nucala™ during pregnancy or within 8 weeks prior to the first day of the LMP. This will be the primary comparison group.

The non-asthmatic unexposed comparison group (Cohort 3) consists of pregnant women who contact the OTIS coordinating center and who have no current diagnosis of asthma and have not been exposed to any known human teratogens (as determined by the OTIS Research Center) for any number of days, at any dose, form the first day of the LMP up to and including the end of pregnancy. This will be a secondary comparison group.

1.3.1 Eligible patient population

Eligibility criteria for the study include the following:

• Residence in the U.S. or Canada at the time of enrollment

• Currently pregnant woman

See protocol for detailed inclusion and exclusion criteria. For specific population for each analysis, see sections 3.2 and 3.3 of this document.

1.3.2 Other population

Not applicable.

1.4 Sample size

The target sample size for the study is 200 women in the exposed cohort; 300 women in the treated disease cohort; and 300 women in the non-asthmatic cohort.

Based on previous experience with the OTIS project, it is estimated that subjects will be an average of 7-10 weeks post-LMP at the time of enrollment. Given this mean gestational timing at enrollment, the anticipated SAB/stillbirth rate is 10%, the estimated elective abortion rate is 5%, and the estimated lost to follow-up rate is 5%.

1.5 Study plan for data collection

The cohort data are collected by telephone at the first intake/enrollment interview, then prospectively at CCI interviews I, II, and the outcome interview. Additional data are collected from obstetric, pediatric, hospital of delivery and specialty physician medical record reviews and questionnaire. See protocol for detailed information about the timeline for data capture.

2. COLLECTED DATA

2.1 Screening log

The study center maintains a record of pregnant women who are eligible and ineligible for the cohort study, as well as a record of eligible pregnant women who decline or consent to enrollment.

2.2 Woman and Infant Data

The intake interview captures information on all medications the woman has taken in pregnancy as well as pregnancy history, family health history, demographic information, and prenatal testing. Following the initial intake interview, participants will be sent a pregnancy diary on which they will be asked to record any additional exposures or events as the pregnancy progresses. Women will be interviewed according to the Study Plan (see section 1.5), to update records of pregnancy exposures and results of prenatal tests, to remind women to maintain the exposure diary, to update phone number and address information, and to determine if the pregnancy has ended prior to the expected due date. The maternal outcome interview will be conducted after the end of the pregnancy.

Data collected from these interviews and the diary include the following:

Intake Interview:

- referral source;
- pregnancy history;
- current health history;
- pre-pregnancy weight and height;
- socioeconomic and demographic: information including maternal and paternal occupation, education and ethnicity; income category;
- medication and supplement use during pregnancy, both prescriptive and over the counter;
- other environmental or occupational exposures;
- alcohol, tobacco, caffeine and illicit drug use;
- current pregnancy complications including illnesses;
- history of onset and other characteristics of asthma, if applicable;
- any pregnancy tests and results;
- names and addresses of health care providers;

CCI Interview(s):

- medication, vaccine, supplement and other exposures prescriptive and over the counter since last interview;
- update records of pregnancy exposures and results of prenatal tests;
- current pregnancy complications including illnesses since last interview;
- remind women to maintain the exposure diary;
- determine if the pregnancy has ended prior to the expected due date.
- update pregnancy tests and results since last interview
- update phone number and address information of health care

Outcome Interview:

1) For live born infants

- date of delivery or end of pregnancy;
- hospital location and mode of delivery;
- sex, birth weight, length and head circumference;
- Apgar scores;

- description of delivery or birth complications including malformations such as any major structural birth defects;
- type and length of hospital stay for mother and infant;
- delivering physician's and infant physician's names and addresses;
- method of infant feeding including breastfeeding and duration of breastfeeding;
- pregnancy weight gain;
- additional exposures and results of prenatal tests occurring since the previous interview;

2) For spontaneous or elective abortions and stillbirths

- date and type of outcome;
- hospital location if applicable;
- prenatal diagnosis;
- pathology results if available;
- additional exposures and results of prenatal tests occurring since the previous interview;
- for stillborn infants: sex, birth size and autopsy results if available.

Data collected from medical records include:

- validation of exposure to Nucala™ – dosage and dates;
- pregnancy outcome;
- prenatal tests and results;
- pregnancy complications;
- mode of delivery;
- birth weight, length and head circumference of infant;
- Apgar scores;
- length and type of hospital stay;
- major structural birth defects in the fetus or child;
- postnatal growth measures for the child, up to 1 year of age;
- evidence of serious adverse events (SAEs) .

3. DEFINITION OF VARIABLES

3.1 Baseline variables

- maternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34);
- paternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34);
- maternal race (Caucasian/White, Black, Asian, Pacific Islander, Native American, Other);
- maternal ethnicity (Hispanic, Non-Hispanic);
- maternal educational category (years of completed education <12, 12-15, >15);
- Hollingshead Socioeconomic Category (1-5);
- family income category (<$10,000, $10,000 - <$50,000, ≥$50,000)
- maternal height (cm);
- maternal Pre-pregnancy body weight (kg);
- maternal pre-pregnancy BMI (kg/m^2) (<18.5, 18.5-24.9, 25-29.9, >=30);
- number of times ever pregnant, including current pregnancy (1, 2-3, 4-5, >=6);

- number of previous live birth or stillbirth deliveries (0, 1-2, 3-4, >=5);
- number of previous pregnancies ending in SAB (0, 1, 2, >=3);
- number of previous pregnancies ending in elective termination (0, 1, 2, >=3);
- gestational age (weeks from first day of LMP of pregnancy at time of enrollment, continuous and categorical (<=13, 13.1-19.9, >=20);
- referral source (OTIS service, Health Care Provider, Internet, Sponsor, Other);
- geographic area of residence (U.S., Canada);
- year of diagnosis with asthma (exposed and disease-frequency-matched cohorts only);
- year of enrollment;
- comorbidities (e.g., depression and anxiety, autoimmune conditions) (yes/no);
- prenatal, multivitamin or folic acid supplement use by timing (began prior to conception, post-conception only, not taken at all);
- alcohol use during pregnancy (yes/no);
- tobacco use during pregnancy (yes/no);
- caffeine use during pregnancy (yes/no);
- prenatal diagnostic tests performed prior to enrollment (ultrasound level 1, ultrasound level 2, chorionic villus sampling, amniocentesis) (yes/no);
- prenatal diagnostic tests performed anytime in pregnancy (ultrasound level 1, ultrasound level 2, chorionic villus sampling, amniocentesis) (yes/no);
- intended/unintended pregnancy (yes/no);
- In Vitro Fertilization (IVF) (yes/no);
- previous child with major structural defect (yes/no);
- previous preterm delivery (yes/no);
- maternal pregnancy exposure to another known human teratogen (e.g., methotrexate) (yes/no);
- exposure to other medications and/or historical exposure to medications such as steroids during pregnancy; (yes/no);
- Global Initiative for Asthma (GINA) classification calculated based on specific medications reported (exposed and diseased comparison cohorts only), collected at each interview during pregnancy.

3.2 Primary endpoint

The primary endpoint will be major structural defects among any pregnancy ending with at least one live born infant. A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.

A major structural birth defect is defined, classified, and confirmed as below:

- Definition: A major structural birth defect is a defect that has either cosmetic or functional significance to the child (e.g., a cleft lip) and is identified up to one year of age by the mother, the health care provider/medical record, or identified in the dysmorphological examination.
- Classification: Major defects are classified according to the Centers for Disease Control and Prevention (CDC)'s MACDP coding manual for major structural defects (CDC. 2017).
- Confirmation of defect: Certain defect requires independent confirmation. For example, a heart murmur thought to represent a ventricular septal defect prior to one year of age will be included if it is confirmed as a heart defect by cardiac ultrasound. Similarly, a midline cutaneous marker at L2-L3 will be included as occult spinal dysraphism only if confirmed by appropriate imaging studies.

3.3 Secondary endpoints

3.3.1 Pregnancy Outcomes:

SAB is defined as non-deliberate embryonic or fetal death that occurs < 20.0 weeks' gestation post-LMP. This applies to women in all 3 cohorts who are enrolled in the study prior to 20.0 weeks' gestation, and only to those in Cohort 1 who are enrolled and exposed prior to 20.0 weeks' gestation. In pregnancies involving multiples with one or more of the outcomes ending in SAB, when there are no live births, the pregnancy is counted as one SAB event; however, when the pregnancy ends in at least one live-born infant, the pregnancy is counted as a live birth outcome.

Elective abortion is defined as deliberate termination of pregnancy at any time in gestation. Reason for elective abortion will be ascertained.

Stillbirth is defined as a non-deliberate fetal death that occurs at or after 20.0 weeks' gestation but prior to delivery. In pregnancies involving multiples with one or more of the outcomes ending in stillbirth, when there are no live births, the pregnancy is counted as one stillbirth event; however, when the pregnancy ends in at least one live-born infant, the pregnancy is counted as a live birth outcome.

Premature delivery is defined as live birth prior to 37.0 weeks' gestation as counted from LMP. This applies to women in all 3 cohorts who are enrolled in the study prior to 37.0 weeks' gestation, and only to those in Cohort 1 who are enrolled and exposed prior to 37.0 weeks' gestation, excluding pregnancies with twins or higher order multiples.

3.3.2 Infant Outcomes:

Small for gestational age (SGA) is defined as birth size (weight, length or head circumference) less than or equal to the 10th percentile for sex and gestational age using National Center for Health Statistics (NCHS) pediatric growth curves for full term infants. Prenatal growth curves specific to preterm infants will be used for premature infants (Olsen et al, 2010). Pregnancies with twins or higher order multiples will be excluded.

Subjects will be considered lost-to-follow-up if they have completed the initial intake interview but subsequently fail to complete the outcome interview despite a standard number of telephone attempts and attempt to contact by mail as per study procedure manual within one year of the mother's estimated due date.

4. STATISTICAL APPROACHES

Table 2. Summary of Exposure Window for Each Outcome

Outcome	Exposure Window
Major Structural Defects	The first day of LMP to the end of the 1st trimester
SAB	The first day of LMP to prior to 20.0 weeks' gestation
Premature Delivery	The first day of LMP to prior to 37.0 weeks' gestation
SGA	The first day of LMP to the end of the pregnancy

4.1 Analyses of baseline characteristics

Baseline characteristics will be summarized within each cohort. For the annual and final reports, all continuous variables will be summarized using the following statistics: Mean, Standard Deviation, Minimum, 1st quartile, Median, 3rd quartile, Maximum. All categorical variables will be summarized using counts and percentages. Missing data or unknown responses will not be counted in the percentages. Comparison will be carried out using two-sample t-tests for continuous variables, and chi-squared or Fisher's exact tests for categorical variables, without adjustment for multiple testing.

4.2 Analyses of primary outcome

For the primary endpoint, the exposure of interest is Nucala™ exposure at any time from the 1st day of the LMP to the end of the first trimester.

The primary comparison will be the rate of major structural defects between the exposed group (Cohort 1) and the diseased comparison group (Cohort 2) among pregnancies resulting in at least one live born infant. A point estimate of the crude (i.e., unadjusted) risk ratio (RR) of the exposed group versus the unexposed group, as well as its 95% confidence interval (CI) will be computed using the normal approximation method. When the expected frequency of any of the cells of the contingency table is less than five, the CI will be obtained by an exact method using the software StatXact; the method is based on inverting an unconditional exact hypothesis test (Agresti and Min, 2001). 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.

4.3 Analyses of secondary outcomes

The analysis of SAB and stillbirth is 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 20.0 weeks of gestation are eligible for the analysis of SAB. Since they are not followed from gestational age zero, survival analysis method will be used to handle left truncation, as well as right-censoring when a subject is lost-to-follow-up prior to 20.0 weeks' gestation. Left-truncated Fleming-Harrington estimate at 20.0 weeks' gestation will be used to estimate the SAB rate in each of the cohorts (Fleming and Harrington, 1991, Pan, 1998). Provided there are sufficient number of events, i.e. at least 10 events per parameter in the regression model, the Cox proportional hazards regression models incorporating left truncation will be used to estimate the hazard ratio (HR) of different cohorts, as well as to obtain the 95% CIs. Stillbirth will be analyzed in a similar fashion.

Preterm Delivery will be analyzed similarly to SAB, as described above, using survival analysis methods to handle possible right-censoring. It applies to women in all 3 cohorts who are enrolled in the study prior to 37.0 weeks' gestation, and only to those in Cohort 1 who are enrolled and exposed prior to 37.0 weeks' gestation, excluding pregnancies with twins or higher order multiples.

SGA at birth weight, height and head circumference, respectively, are binary endpoints. The analysis of each of these outcomes will be similar to the analysis of the primary outcome, based on all pregnancies resulting in live born infants excluding twins or higher order multiples.

5. FINAL ANALYSIS

Analyses of data at the conclusion of the study will be performed according to the methods as described in Section 4.

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

6. MISSING DATA

Missing values typically occur in less than 5% of the cases for any single covariate (Chambers et al., 2019).

For the outcome of SAB, for some cases the exact date of SAB might be unknown, and instead a window for possible SAB time is available. This is known as interval censored data, and can also be handled using MI (Pan W, 2000). An exact SAB time will be imputed by sampling uniformly from the corresponding time window.

The number of above imputations will be 10, i.e., 10 datasets with imputed data will be created. Each imputed data set gives a point estimate of the regression coefficients as well as its standard deviation, which will be combined across the 10 datasets to obtain the final estimate of the causal RR/HR and their 95% CI's (Little and Rubin, 2002).

7. CCI [redacted] ANALYSIS

There will be no formal CCI [redacted] comparative analysis performed. However, summary data will be reported on an annual basis until each phase of the final analyses are performed.

8. SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be performed using the current version of open-source statistical programming language R and STATXACT.

9. REFERENCE

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