Redacted Protocol Study J2T-MC-B005

Lebrikizumab Exposure During Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry

Confidential Information

Protocol Electronically Signed and Approved by Lilly: approval date provided below

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Post-Authorization Safety Study (PASS)

Title	Lebrikizumab Exposure During Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry
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Marketing Authorization Holder(s)	Eli Lilly and Company
Joint PASS	No
Research Question and Objectives	The objective of this study is to assess pregnancy and infant outcomes among women who become pregnant while exposed to lebrikizumab relative to the outcomes in 2 matched comparator populations. The outcomes are major structural defects identified in children up to 1 year of age, as well as rate of spontaneous abortion, elective termination/abortion, stillbirth, preterm delivery, a pattern of minor structural birth defects, small for gestational age at birth, small for age for postnatal growth at 1 year of age, serious infections up to 1 year of age, developmental milestones, and neonatal death.
Country(ies) of study	US and Canada
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Abbreviations: No = number; PAS = post-authorization study; PASS = post-authorization safety study.

Marketing Authorization Holder

Marketing Authorization Holder (MAH)	Eli Lilly and Company, Indianapolis, IN 46285, USA
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2. List of Abbreviations

Term	Definition
AD	atopic dermatitis
AE	adverse event
AR	adverse reaction
ASQ	Ages and Stages Questionnaire
CDC	Centers for Disease Control
CI	confidence interval
DOC	date of conception
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
IL	interleukin
IRB	Institutional Review Board
LMP	last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MTB	MotherToBaby
OTIS	Organization of Teratology Information Specialists
POEM	Patient Oriented Eczema Measure
PS	propensity score
RR	relative risk
SAB	spontaneous abortion
SAE	serious adverse event
SAP	Statistical Analysis Plan

SGA	small for gestational age
UCSD	University of California San Diego

3. Responsible Parties

Function	Name	Title	Affiliation	Address
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PPD Pharmacoepidemiology	PPD	PPD	Eli Lilly and Company (Sponsor)	Lilly Corporate Center Indianapolis, IN 46285

Abbreviation: OTIS = Organization of Teratology Information Specialists.

4. Abstract

- **Title:**

  Lebrikizumab Exposure During Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry

- **Rationale and background**

  The Pregnancy Exposure Registry is sponsored by Eli Lilly and Company (Lilly), conducted by the OTIS Research Group, and administered by investigators at the coordinating site located at the UCSD.

  This OTIS Pregnancy Registry is a US-based registry designed to monitor pregnancy and infant outcomes among women in the US and Canada exposed to lebrikizumab for the treatment of AD and comparison group of pregnant women with AD who have not used lebrikizumab during pregnancy. As of May 2025, lebrikizumab has been approved in the US and Canada for the treatment of moderate-to-severe AD. Should other indications for lebrikizumab be approved over the course of the study, patients with these indications will be eligible for enrolment.

  Pregnant women with exposure to lebrikizumab for the treatment of moderate-to-severe AD, or any approved indication, and comparison pregnant women with AD, or any lebrikizumab-approved indication, but who have not used lebrikizumab during pregnancy are eligible for inclusion in the registry.

  There are insufficient data to evaluate if there is an increased risk of major birth defects, SAB, pattern of minor malformations, or adverse maternal or fetal outcomes with exposure to lebrikizumab during pregnancy.

  Due to insufficient data on the effects of lebrikizumab exposure during pregnancy, a postmarketing registry is an important component of epidemiologic research on the safety of this medication. The goal of the registry is to conduct an observational, prospective cohort study that will involve collecting pregnancy outcome and follow-up of live born infants up to 1 year of age. The Registry fulfills a postmarketing requirement from the US FDA.

- **Research question and objectives**

  Research Question: Is the risk of pregnancy and infant adverse outcomes increased among pregnant women in the Organization of Teratology Information Specialists (OTIS)/ MotherToBaby Pregnancy Registry (OTIS Pregnancy Registry) who were exposed to lebrikizumab during pregnancy compared with those who were not exposed to lebrikizumab during pregnancy?

  Objective: To assess whether pregnant women with AD who were exposed to lebrikizumab during pregnancy experienced increased risk of pregnancy and infant

adverse outcomes, including major structural birth defects, SAB, elective termination/abortion, stillbirth, preterm delivery, a pattern of minor structural malformations, SGA, small for age postnatal growth at 1 year of age, serious infections up to 1 year of age, developmental milestones, and neonatal death, relative to 2 comparator groups of pregnant women with AD not exposed to lebrikizumab within 5 half-lives (123 days) prior to the estimated DOC or during the pregnancy. These 2 comparator groups include

(1) a primary comparison group of women with AD exposed to phototherapy, or other systemic therapy, except IL-13–targeting biologics, for the treatment of an approved indication within 5 half-lives prior to the estimated DOC or during the pregnancy, and
(2) a secondary comparison group of women with AD who may or may not have received treatment for a lebrikizumab-approved indication but who have not been exposed to phototherapy or systemic therapy for the within 5 half-lives prior to the estimated DOC or during the pregnancy.

Outcomes

The primary outcome of the study is major structural defects in children up to 1 year of age.

The secondary outcomes of the study are

- SAB/miscarriage
- stillbirth
- elective termination/abortion
- preterm delivery
- pattern of 3 or more minor structural defects
- SGA
- postnatal growth of live born children up to 1 year of age
- serious infections in live born children up to 1 year of age
- developmental milestones in live born children at 12 months of age, and
- neonatal death.

- **Study design**

  This proposed study is a prospective, observational cohort study of pregnancy and infant adverse outcomes in pregnant women with exposure to lebrikizumab using data from the OTIS Pregnancy Registry. The birth prevalence/incidence rates of pregnancy outcomes and incidence proportion of the infant outcome for women with AD exposed to any dose of lebrikizumab anytime in pregnancy or within 5 half-lives (123 days) prior to the estimated DOC will be compared to those observed in 2 comparator cohorts that are not exposed to lebrikizumab within 5 half-lives. The first comparator group consists of

pregnant women with AD who have been treated with phototherapy or systemic therapy, except IL-13–targeting biologics, anytime in pregnancy or within 5 half-lives prior to the estimated DOC. The second comparator group consists of pregnant women with AD who may or may not have received treatment but have not been exposed to phototherapy or systemic therapy for an approved indication anytime in pregnancy or within 5 half-lives prior to the estimated DOC. Pregnant women exposed to lebrikizumab who do not meet the inclusion criteria of this study may be followed as part of an "exposure series." All women will be recruited via voluntary participant registration following informed consent into the OTIS registry. Participants may withdraw from the study at any time.

- **Population**

  The study population includes pregnant women who reside in the US or Canada.

  The 3 groups of women enrolled and followed for pregnancy and infant outcomes include:

  (1) Pregnant women with AD and who have received at least 1 dose of lebrikizumab anytime during pregnancy or within 5 half-lives (123 days) prior to the estimated DOC.
  (2) Pregnant women with AD exposed to phototherapy or systemic therapy, other than IL-13–targeting biologics, during pregnancy or within 5 half-lives prior to the estimated DOC (primary comparator).
  (3) Pregnant women with AD who may or may not have received treatment for AD but who have not been exposed to any dose of lebrikizumab, phototherapy, or systemic therapy within 5 half-lives prior to the estimated DOC (secondary comparator).

  Pregnant women exposed to lebrikizumab who do not meet the eligibility criteria (see eligibility criteria) of this study may be followed separately as part of an exposure series.

- **Variables**

  Lebrikizumab exposure variables: Exposure will be defined as treatment with lebrikizumab anytime during pregnancy or within 5 half-lives (123 days) prior to the estimated DOC obtained by maternal report and verified by medical record review, when available, with detailed information on the gestational timing, route of administration, dose, and dates of administration.

  Pregnancy outcomes of interest include SAB/miscarriage, stillbirth, elective termination/abortion, and preterm delivery.

  Infant outcomes of interest include infant birth size, major structural defects, postnatal growth of live born children to 1 year of age, serious infections to 1 year of age, developmental milestones, a pattern of 3 or more minor structural malformations, and neonatal death.

Information on study outcomes will be obtained by maternal report/questionnaire, obtained by dysmorphology physical examination, obtained or verified by medical record review when available, or a combination of the listed.

Potential confounders or covariates to be collected include, but are not limited to, maternal age, race/ethnicity, socioeconomic status, pregnancy and health history, lifestyle factors such as tobacco and alcohol use, comorbidities, medication use, vaccine and vitamin/mineral exposures, maternal infections, and prenatal tests. Measures of disease severity/symptom control for the lebrikizumab indication will be collected for those enrolled in the lebrikizumab-exposed and disease-matched cohorts. Details regarding definitions are provided in the SAP.

- **Data sources**

  This study will use data collected as part of the OTIS Pregnancy Registry from maternal interviews, medical records (obstetric, delivery hospital, pediatric, other specialty provider if applicable, or a combination of the listed), and pregnancy exposure form.

  In addition, the POEM (Charman et al. 2004) assessing disease severity/activity is administered to participants with AD.

- **Study size**

  The cohort study target sample size is 500 pregnant women: 100 pregnant women who have been exposed to at least 1 dose of lebrikizumab for AD during pregnancy or within 5 half-lives (123 days) prior to the estimated DOC; 200 pregnant women with AD and exposed to phototherapy, systemic therapy, other than an IL-13–targeting biologic, or both for the treatment of AD during pregnancy or within 5 half-lives prior to the estimated DOC (primary comparator); and 200 pregnant women with AD who may or may not have received treatment for AD but who have not received any dose of an IL-13–targeting biologic, phototherapeutic, or systemic therapy for the treatment of AD during pregnancy or within 5 half-lives prior to the estimated DOC (secondary comparator).

- **Data analysis**

  The distributions of demographic and baseline characteristics will be summarized within the exposure and comparator cohorts. The following measures will be calculated for the pregnancy and infant outcomes: birth prevalence of major structural birth defects; incidence rates of SAB, elective termination/abortion, stillbirth, and preterm delivery; and incidence proportions of SGA, small for age postnatal growth at 1 year of age, serious infections to 1 year of age, developmental milestones, and neonatal death. For each outcome, risk estimates will be described separately for the lebrikizumab exposure cohort and the comparator cohorts. The outcomes will be compared between the lebrikizumab-exposed cohort and the primary comparator cohort, and between the lebrikizumab-exposed cohort and the secondary comparator cohort.

Statistical analyses of those enrolled who do not meet the cohort study criteria will be descriptive only; these cases constitute the "exposure series." All relevant exposure, outcome, and covariate data within each study group will be summarized using descriptive statistics annually. Mean, standard deviation, median, maximum, and minimum values will be presented for continuous variables while frequencies and percentages will be presented for categorical variables

- **Milestones**

  The study is planned for approximately 10.5 years from the enrollment of the first participant in (01 December 2025) until completion of data collection. There will be 8 years of active recruitment, with an annual interim report reviewed by the Scientific Advisory Board each year. The final report with statistical analysis according to the SAP will be prepared at the end of the study (30 June 2036).

5. Amendments and Updates

Version Number	Date	Section of Study Protocol	Amendment or Update	Rationale for Update
2	Please see page 1	Appendix 2	Inserted content of Appendix 2 (non-substantial amendment).	Correcting inadvertently missing content.
2	Please see page 1	Throughout the protocol	Minor typographical corrections and formatting.	Consistency throughout the protocol.

6. Milestones

Milestone	Planned date
Start of data collection	01 December 2025
End of data collection	31 December 2035
Registration in the EU PAS register	No later than 1 day prior to start of data collection
Final report of study results submission	30 June 2036

Abbreviation: PAS = post-authorization study.

7. Rationale and Background

Clinical trials evaluating the efficacy and safety of lebrikizumab in patients with moderate to severe AD have demonstrated significant improvements in disease severity, pruritus, and quality of life compared to placebo, with a favorable safety profile observed in clinical studies (Silverberg et al. 2023). Lebrikizumab works by blocking the activity of IL-13, thereby interrupting the inflammatory cascade and restoring skin barrier function. Its mechanism of action is distinct from that of other biologic agents targeting IL-4 or IL-13 receptors, offering a unique therapeutic approach for patients with AD who are candidates for systemic therapy (Guttman-Yassky et al. 2020).

Despite the efficacy and safety data from clinical trials, uncertainties remain regarding the safety and potential risks of lebrikizumab use during pregnancy (Napolitano et al. 2021). Pregnant women were not included in the lebrikizumab clinical development program, or participants were discontinued from the trials if they became pregnant during the course of the study. Pregnancy introduces additional considerations for drug safety, as physiological changes such as altered drug metabolism, increased plasma volume, and placental transfer can impact maternal and fetal outcomes (Sachdeva et al. 2009). The pharmacokinetics and pharmacodynamics of lebrikizumab during pregnancy in humans has not been studied and no information is currently available to determine a dose-response relationship during pregnancy for lebrikizumab. The results from animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (Ebglyss US prescribing information, 2024). For example, animal reproduction studies showed no effects on embryo-fetal development after subcutaneous administration of lebrikizumab to cynomolgus monkeys during organogenesis at doses up to 18 times the human exposure at the maximum recommended dose. Similarly pre- and post-natal development studies demonstrated no evidence of teratogenicity, abnormal growth, or development in dams and nursing offspring through 6 months of age.

Due to lack of data, it is not known whether lebrikizumab can affect pregnancy and infant outcomes in humans. Lilly is sponsoring an observational study, conducted by the OTIS, to evaluate pregnancy and infant outcomes among pregnant women enrolled in the MTB North American pregnancy registry who are exposed to any dose of lebrikizumab within 123 days prior to the estimated DOC (5 half-lives of lebrikizumab) or anytime during pregnancy. In general, 5 times the half-life of a drug is considered as an average of the time needed to eliminate a drug from the body, although it can vary from person to person depending on a number of patient and drug variables (Rittler et al. 2008). Exposure during pregnancy is, in this study, defined as drug administration of any dose within 5 half-lives of the given drug prior to the estimated DOC and anytime in pregnancy.

This noninterventional study is designated as a post-authorization safety study and is designed to meet a postmarketing requirement from the FDA.

8. Research Question and Objectives

Is the risk of pregnancy and infant adverse outcomes increased among pregnant women in the Organization of Teratology Information Specialists (OTIS)/ MotherToBaby Pregnancy Registry (OTIS Pregnancy Registry) who were exposed to lebrikizumab during pregnancy compared with those who were not exposed to lebrikizumab during pregnancy?

The objective is to assess whether pregnant women who were exposed to lebrikizumab during pregnancy experienced increased risk of specified pregnancy and infant adverse outcomes, relative to 2 comparator groups of pregnant women with AD:

1) a primary comparator group of pregnant women exposed to any dose of phototherapy or other systemic therapy for the treatment of AD within 5 half-lives prior to the estimated DOC or anytime in pregnancy (details in Section 9.2.2), and
2) a secondary comparator group of pregnant women with AD who may or may not have received treatment for AD but who have not been exposed to any dose of phototherapy or systemic therapy within 5 half-lives prior to the estimated DOC or anytime during pregnancy for the treatment of AD.

The primary outcome of the study is major structural birth defects.

The secondary outcomes of the study are

- Pregnancy outcomes:
  - SAB/miscarriage
  - Stillbirth
  - Elective termination/abortion
  - Preterm delivery
- Infant outcomes:
  - SGA
  - Pattern of 3 or more minor structural malformations
  - Postnatal growth of live born children at 1 year of age
  - Serious infections up to 1 year of age
  - Developmental milestones at 12 months of age
  - Neonatal death

9. Research Methods

9.1. Study Design

This proposed study is a prospective, observational cohort study of pregnancy and infant outcomes among pregnant women exposed to any dose of lebrikizumab within 5 half-lives prior to the estimated DOC or anytime during pregnancy, enrolled into the OTIS Lebrikizumab Pregnancy Registry. The prevalence of outcomes in women exposed to any dose of lebrikizumab and their infants will be compared to those observed in 2 unexposed comparator groups: pregnant women with AD and exposed to phototherapy, systemic therapy, except an IL-13–targeting biologic anytime from 5 half-lives prior to the estimated DOC or anytime during pregnancy (primary comparator), or both and pregnant women with AD who may or may not have received treatment for AD but who have not been exposed to any phototherapy or systemic therapy for the treatment of AD within 5 half-lives prior to the estimated DOC or anytime during pregnancy (secondary comparator). The primary comparator is expected to be most comparable to the lebrikizumab-exposed cohort because it includes women with a similar need for phototherapy or systemic therapy for the treatment of AD. The secondary comparator may include women with less severe AD than the lebrikizumab-exposed cohort but may include women with similar disease severity who have elected to forgo treatment in pregnancy. Although the registry will follow-up on all pregnancies exposed to lebrikizumab, including those who do not qualify for the cohort (exposure series), the core of the registry will be a prospective, observational cohort study. Enrollment is voluntarily and takes place once the woman provides informed consent to participate in the OTIS Registry. Participants may withdraw from the study at any time.

The pregnancy outcomes are major structural birth defects, SAB, elective termination/abortion, stillbirth, and preterm delivery; the infant outcomes are a pattern of minor structural malformations, SGA small for age postnatal growth at 1 year of age, serious infections to 1 year of age, developmental milestones, and neonatal death. The target sample size for the study is 500 pregnant women: 100 pregnant women in the lebrikizumab exposure cohort and 200 pregnant women in each of the comparator cohorts. Up to an additional 50 women may be enrolled into the lebrikizumab exposure-series. The main measures of effect are unadjusted and adjusted RRs and their 95% CIs comparing the exposed cohort to the comparator cohorts for the outcomes of major structural birth defects, SGA, and postnatal growth, and unadjusted and adjusted hazard ratios and 95% CIs comparing the exposed cohort to the comparator cohorts for the outcomes of SAB, elective termination/abortion, stillbirth, and preterm delivery.

At the end of the fourth year of the registry, an interim assessment of participant accrual will be conducted to determine the feasibility of continuing the pregnancy registry. Projections will be made to estimate the number of live births expected over the remaining recruitment years in order to determine the feasibility of continuing the pregnancy registry. At this point, a determination of whether it is likely or unlikely for the study to be completed as designed will be made with the advice of the external Scientific Advisory Board.

9.2. Setting

The registry cohort study will be conducted by the OTIS, which is a network of university- and health department–based telephone information centers serving pregnant women and HCPs throughout North America (Leen-Mitchell et al. 2000). These services receive spontaneous telephone inquiries from women and HCPs 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 HCP callers free of charge. These services also provide a basis for collaborative research such as this registry. Thus, individual Teratogen Information Services located throughout the US and Canada will serve as a source of referrals not only for lebrikizumab-exposed pregnancies but also for similarly ascertained disease-matched comparison pregnant women who have not used lebrikizumab in pregnancy. Further description of recruitment and awareness towards the registry is described in Section 9.4.1.

OTIS member services receive over 70,000 teratogen information inquiries per year, therefore OTIS members constitute a major source of identification and recruitment of exposed women and appropriate comparison women. Once women are in contact with the Registry Research Coordinating Center, enrollment in the registry is voluntary and requires informed consent of the pregnant woman. The registry encourages enrollment as early in the pregnancy as possible, before any prenatal testing results are known. This is accomplished by encouraging clinicians to refer patients and patients who contact an OTIS service or who self-refer to enroll upon first positive pregnancy test. These efforts reduce possible bias based on prior knowledge of a normal or abnormal ultrasound and allow for better estimation of risk of SAB.

9.2.1. Study Period

The study is planned for about 10.5 years from the enrollment of the first participant in until study completion (completion of final report). There will be 8 years of active recruitment, with an annual report reviewed each year by the independent Scientific Advisory Board managed by OTIS. The annual report will also be provided to Lilly. At the end of the fourth year of the registry, an interim assessment of participant accrual will be conducted to determine the feasibility of continuing the pregnancy registry. The final report with statistical analyses according to the SAP will be prepared at the end of the study.

Pregnant women will be followed throughout their pregnancy, and pregnancy outcome information will be collected. Live born infants will be followed through 1 year of age.

9.2.2. Eligibility Criteria

The prospective cohort study will enroll pregnant women in 3 cohorts. Eligibility for the cohort study includes the following:

1) Currently pregnant at the time of enrollment
2) Residence in the US or Canada at the time of enrollment

3) Verbal informed consent to participate in OTIS Pregnancy Registry and agreement to the conditions and requirements of the study including the interview schedule, dysmorphology exam, developmental screening, and release of medical records
4) Current diagnosis of AD at the time of enrollment, validated by medical records when possible. If other indications for lebrikizumab should be approved over the course of the study, pregnant women with these indications will be eligible for enrollment

9.2.2.1. Inclusion Criteria

Women must meet all the criteria listed under the respective cohorts to enroll in that particular cohort of the registry:

Cohort 1: lebrikizumab – exposed cohort

1) Exposure to lebrikizumab for any number of days, at any dose, and at any time from 5 half-lives prior to the estimated DOC (123 days) or during pregnancy

Cohort 2: AD Comparator I – phototherapy or systemic treatment

1) Exposed to phototherapy, systemic therapy, or both for the treatment of AD (Appendix 1), or another approved indication, for any number of days, at any dose, and at any time within 5 half-lives prior to the estimated DOC or during pregnancy

Cohort 3: AD Comparator II – without phototherapy or systemic treatment

1) May or may not have received treatment for AD or another approved lebrikizumab indication but who have not been exposed to any dose of phototherapy or systemic therapy for the treatment of AD or another approved indication within 5 half-lives prior to the estimated DOC or any time during pregnancy

9.2.2.2. Exclusion Criteria

Pregnant women meeting any of the following criteria will not be included in the cohort study:

Cohort 1: lebrikizumab-exposed cohort

1) Enrollment in the lebrikizumab cohort study with a previous pregnancy
2) Exposure to any dose of another IL-13–targeting biologic within 5 half-lives prior to the estimated DOC or anytime during pregnancy
3) Retrospective enrollment after the outcome of pregnancy is known (that is, the pregnancy has ended prior to enrollment)
4) Results of a diagnostic test are positive for a major structural birth defect prior to enrollment. However, women who have had any normal or abnormal prenatal screening or diagnostic test prior to enrollment are eligible as long as the test result does not indicate a major structural birth defect

Cohort 2: AD therapy comparator I – phototherapy or systemic treatment

1) Enrollment in the lebrikizumab cohort study with a previous pregnancy
2) Exposure to any dose of lebrikizumab or another IL-13–targeting biologic within 5 half-lives prior to the estimated DOC or anytime during pregnancy

3) Retrospective enrollment after the outcome of pregnancy is known (that is, the pregnancy has ended prior to enrollment)
4) Results of a diagnostic test are positive for a major structural defect prior to enrollment. However, women who have had any normal or abnormal prenatal screening or diagnostic test prior to enrollment are eligible as long as the test result does not indicate a major structural defect

Cohort 3: AD therapy Comparator II – without phototherapy or systemic treatment

1) Enrollment in the lebrikizumab cohort study with a previous pregnancy
2) Exposure to any dose of lebrikizumab or another IL-13–targeting biologic within 5 half-lives prior to the estimated DOC or anytime during pregnancy
3) Exposure to any dose of phototherapy, systemic therapy for the treatment of AD, or both, or another lebrikizumab-approved indication, within 5 half-lives prior to the estimated DOC or during pregnancy
4) Retrospective enrollment after the outcome of pregnancy is known (that is, the pregnancy has ended prior to enrollment)
5) Results of a diagnostic test are positive for a major structural defect prior to enrollment. However, women who have had any normal or abnormal prenatal screening or diagnostic test prior to enrollment are eligible as long as the test result does not indicate a major structural defect

9.2.2.3. Lebrikizumab-Exposed Pregnancies Not Eligible for the Lebrikizumab-Exposed Prospective Cohort

By study design, pregnancies with lebrikizumab exposure that do not meet the exposed cohort (Cohort 1) criteria for reasons described in Section 9.2.2.2 will be excluded from the cohort analysis and will be presented in a descriptive analysis only; however, information on birth outcomes can be obtained and can be useful when reviewing the cohort data for any evidence of increased risks for the study outcomes. For this reason, women who do not meet the exposed cohort criteria will be included in the Exposure Series. Women who are eligible for enrollment in the Exposure Series include, but are not limited to, the following: exposure to lebrikizumab during pregnancy for an indication other than an approved indication, women who enrolled with a previous pregnancy in the cohort, and retrospective reports of a lebrikizumab-exposed pregnancy after the outcome of pregnancy is known (that is, the pregnancy has ended prior to enrollment or results of a diagnostic test are positive for a major structural birth defect prior to enrollment). With informed consent, data will be collected from those enrolled in the Exposure Series from maternal interviews and medical record review using the same protocol as the cohort study to the extent possible.

9.2.2.4. Analysis Populations

The registry will collect and follow-up on reports of all types (that is, retrospective, exposure after first trimester only, off-label indication, and so on; see Section 9.2.2.3) involving pregnancy exposure to lebrikizumab; however, the core of the registry will be a prospective cohort study

designed to ascertain and follow-up on pregnancy exposures to lebrikizumab and to compare these outcomes to 2 internally generated comparator groups:

- Comparator Group 1 consisting of pregnant women with AD and exposed to any dose of phototherapy, systemic therapy other than lebrikizumab or another IL-13–targeting biologic for the treatment of an approved indication within 5 half-lives prior to the estimated DOC or during pregnancy, or both. This will be the primary comparator group.
- Comparator Group 2 consisting of pregnant women with AD who may or may not have received treatment for AD but who have not been exposed to any dose of lebrikizumab or another IL-13–targeting biologic, phototherapeutic, or systemic therapy for the treatment of AD within 5 half-lives prior to the estimated DOC or during pregnancy. This will be a secondary comparator group.

Differences between the cohorts for key demographics, such as maternal age, socioeconomic status, and race/ethnic distribution, will be monitored annually. Should they occur, they will be addressed in future recruitment efforts and in the statistical analysis phase of the study through methods such as adjustment, detailed in the SAP.

9.2.3. Follow-Up

Pregnant women are entered in a cohort at the time of enrollment into the OTIS Pregnancy Registry. Information is collected on their pregnancy to date, and they are then followed for the duration of their pregnancy. In addition, infants will be followed for potential safety events through their first year of life. Follow-up will end at the earliest of the following events:

- Lost to follow-up, that is, an enrolled individual who withdraws or who fails to complete the outcome interview despite a standard number of telephone attempts and attempt to contact by mail as per study procedure manual within 1 year of the participant's estimated due date
- Occurrence of SAB, elective termination/abortion, or stillbirth
- End of follow-up (that is, 1-year postpartum)
- End of study period
- Neonatal or infant death, or
- Maternal death during pregnancy.

9.3. Variables

Key exposure, outcome, and potential confounding variables are defined below in Table 9.1. Data on these variables will be collected via maternal interview and medical record review per standard process described in the OTIS Pregnancy Registry protocol. Detailed operational definitions will be provided in the SAP.

9.3.1. Identification of Exposure and Comparator

Exposure and disease data are obtained by maternal report, medical record, or both to classify exposure and disease status. The 2 sources of information are used in order to minimize misclassification of exposure and disease status. Detailed information regarding exposures and medical history of participants is obtained through the maternal interviews, including at enrollment, at interim time points during pregnancy, and at the pregnancy outcome interview (0 to 6 weeks after the expected due date or end of pregnancy). Participants are directly queried about the exposure to lebrikizumab, including information on the gestational timing, and dates of administration, as well as medical history, including diagnosis of AD. Exposures are coded using the Slone Drug Dictionary. Medical history is entered from a drop-down list of conditions. In addition, medical records from the obstetric provider, hospital of delivery, and any specialty provider are reviewed, when available, for all participants.

A participant is classified as unexposed to lebrikizumab if she reports that she did not receive lebrikizumab from 5 half-lives prior to the estimated DOC or anytime during pregnancy, and her medical record, when available, shows no indication that she received lebrikizumab during this time. A participant is classified as exposed to lebrikizumab if she reports in the maternal interviews that she received any dose of lebrikizumab from 5 half-lives prior to the estimated DOC or anytime during pregnancy or if there is supporting documentation in the medical record and that information is confirmed through maternal report. If maternal report indicates no receipt of lebrikizumab but the medical record indicates discordance, the participant is contacted for reconciliation. Moreover, where maternal report indicates that lebrikizumab was received but documentation in the medical record is discordant (that is, no indication in medical record that lebrikizumab was administered), the maternal report would supersede medical record for classification as exposed.

The estimated gestational weeks to qualify women for the study for exposure is based on weeks from the estimated DOC and to classify outcomes is based on weeks from the first day of LMP, which is counted as Day 0. In circumstances where the date of LMP is not available or uncertain, or when a prenatal ultrasound estimates a gestational week that is discrepant according to obstetric guidelines, gestational week of pregnancy will be assigned based on the earliest available ultrasound (ACOG 2017).

Table 9.1 below provides a description of variables for exposures to be included in this study. Each pregnancy and infant outcome will be analyzed separately, and the following exposure and comparator cohorts will be defined separately for each outcome analysis, depending on a participant's timing of exposure/study enrollment as it relates to the at-risk period for that specific outcome:

- **Lebrikizumab Exposure**
  - Exposure to any dose of lebrikizumab from 5 half-lives prior to the estimated DOC (123 days) or during pregnancy
  - Diagnosed with AD or any approved indication of lebrikizumab

  - Not exposed to any dose of another IL-13–targeting biologic within 5 half-lives prior to the estimated date of conception or during pregnancy

- **AD Therapy Comparator I – Phototherapy or Systemic Treatment**
  - Not exposed to any dose of lebrikizumab or another IL-13–targeting biologic within 5 half-lives prior to the estimated date of conception or during pregnancy
  - Exposure to any dose of phototherapy, systemic AD treatment, or both; or other lebrikizumab-approved indication, other than lebrikizumab; or another IL-13–targeting biologic within 5 half-lives prior to the estimated date of conception or during pregnancy
  - Diagnosed with AD or any another lebrikizumab-approved indication
- **AD Therapy Comparator II – Without Phototherapy or Systemic Treatment**
  - Not exposed to any dose of lebrikizumab; another IL-13–targeting biologic, phototherapy, or any other systemic therapy for the treatment of AD; or other lebrikizumab-approved indication within 5 half-lives prior to the estimated date of conception or during pregnancy
  - Diagnosed with AD or another lebrikizumab-approved indication

9.3.2. Classification of Pregnancy and Infant Outcomes

The following pregnancy and infant outcome variables (refer to Table 9.1) are obtained by maternal report, medical record review, when available, or both as part of existing procedures for the pregnancy registry.

9.3.3. Major Structural Birth Defects

The method for classifying major structural birth defects for purpose of analysis has been described by the study investigators and the OTIS Research Group (Chambers et al. 2001; CDC 2023) and has been used in previous studies conducted by OTIS.

A major structural birth defect is defined as a defect that has either cosmetic or functional significance to the child (for example, a cleft lip). Major structural birth defects diagnosed during pregnancy and up to 1 year of age are reported by participants or are identified through medical record review. Independent confirmation of certain defects is required via medical record review. For example, a heart murmur thought to represent a ventricular septal defect prior to 1 year of age will be included if it is confirmed as a heart defect by cardiac ultrasound. Similarly, a midline cutaneous marker that is noted at L2-L3 will be included as occult spinal dysraphism only if confirmed by appropriate imaging studies.

Classification of major structural birth defects is performed uniformly across cohorts according to the CDC MACDP coding criteria (CDC 2023).

- Some major structural birth defects are known consequences of pregnancy events, such as preterm delivery, and are therefore not directly due to medication exposure. For example, isolated patent ductus arteriosus or isolated inguinal hernia in an infant delivered before 36 weeks' gestation are considered consequences of prematurity, and therefore, using CDC coding criteria, neither of these defects would be counted as major structural birth defects. Other structural defects, such as club foot or cranial synostosis, could be due to position of the infant in the uterus or could be primary defects initiated earlier in pregnancy. In most cases, it is not possible to know the true onset or etiology of the defect. Therefore, using CDC coding criteria, these defects are counted as major structural birth defects uniformly across all cohorts.

Major structural birth defects identified by prenatal ultrasound or examination of the products of conception following elective termination/abortion or SAB will not be included in the primary analysis (risk of major structural birth defects among pregnancies ending in at least 1 live birth) due to potential bias involved in nonuniform use of prenatal diagnosis and pathology evaluation for all abortuses. For the primary analysis, chromosomal defects will be excluded. Chromosomal defects will be included as part of the overall baseline risk of birth defects in a sensitivity analysis.

As per recommendations in the FDA Draft Guidance for Industry Postapproval Pregnancy Safety Studies (FDA 2019), an expert clinical teratologist/dysmorphologist and coinvestigator for OTIS Pregnancy Registry studies reviews all the medical records and reports of major structural birth defects. The review is done blinded to exposure status and performed in the same manner for exposed and comparator cohorts.

When major structural birth defects are reported, an adjudication process is used for classification of those defects. First, suspected defects are classified by the OTIS study manager once all efforts have been made to obtain adequate information from the mother and infant's HCPs. All major structural birth defects are then reviewed in detail by the study coinvestigator and expert teratologist on this study.

If additional consultation is required for adjudication or classification, the study investigators may consult with the medical director of the CDC's MACDP and members of the study's external Scientific Advisory Board. These consultants are also blinded to exposure information at the time of the classification review. After classification has been completed, at each annual interim and final Scientific Advisory Board meetings for the study, the listing of major structural birth defects is reviewed. The members of the Scientific Advisory Board, who are experts in major structural birth defects, as part of the review process, may ask for additional information regarding classification of major structural birth defects. However, at the time of the annual report review, the Scientific Advisory Board members are not blinded to exposure. The final adjudication of the classification of major structural defects is made through this multi-step process and all data presentations derived from the study will clearly describe the adjudication process (Section 13).

9.3.3.1. Spontaneous Abortion
Defined as nondeliberate fetal death that occurs prior to 20 weeks from the first day of LMP.

9.3.3.2. Elective Termination/Abortion
Defined as deliberate termination of pregnancy at any time in gestation. Reasons for elective termination/abortion are captured and are classified as due to medical reasons or nonmedical reasons.

9.3.3.3. Stillbirth
Defined as nondeliberate fetal death any time in gestation at or after 20 weeks from the first day of LMP.

9.3.3.4. Preterm Delivery
Defined as live birth prior to 37 weeks' gestation as counted from the first day of LMP.

9.3.3.5. SGA at Birth
Defined separately for weight, length, and head circumference (binary endpoints) as birth size less than the 10th centile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm infants (CDC 2000; Olsen et al. 2010).

9.3.3.6. Small for Age Postnatal Growth at 1 Year of Age
Defined separately for weight, length, and head circumference (binary endpoints) as postnatal size less than the 10th centile for sex and age using National Center for Health Statistics pediatric growth curves and adjusted postnatal age for preterm infants if the postnatal measurement is obtained at less than 1 year of age (CDC 2000).

9.3.3.7. Pattern of Minor Structural Defects
Defined as a pattern of 3 or more minor structural defects occurring in at least 2 children in the exposed cohort and identified by a study examiner based on the study-related physical examination.

9.3.3.8. Serious Infections
Defined as any infection requiring hospitalization identified in live born infants up to 1 year of age.

9.3.3.9. Developmental Milestones
Defined as 1 or more domains scored as abnormal on the ASQ-3 completed by the mother when the infant is approximately 12 months of age, adjusted for premature delivery.

9.3.3.10. Neonatal Death
Defined as death of live born infant within 28 days of delivery.

Table 9.1. Exposure, Comparator, Exclusion, and Outcome Variables

Variable	Role	Data Source(s)	Operational Definition
Exposure to lebrikizumab	Exposure	Maternal report Medical record	Maternal report of exposure to lebrikizumab of at least 1 dose any time from 5 half-lives (123 days) prior to the estimated date of conception, and anytime in pregnancy up to the end of pregnancy. Confirmation of exposure with medical records when available.
Dose of lebrikizumab	Exposure	Maternal report Medical record	Dose of lebrikizumab (maternal report and confirmation with medical records) when available.
Duration of lebrikizumab use	Exposure	Maternal report Medical record	Number of weeks when any dose of lebrikizumab was received in the period from 5 half-lives (123 days) prior to the estimated date of conception through the end of pregnancy (maternal report and confirmation with medical records) when available.
Indication	Exposure	Maternal report Medical record	Indication for use of lebrikizumab (maternal report and confirmation with medical records) when available.
Gestational age at time of initial exposure to lebrikizumab	Exposure	Maternal report Medical record	Dates of exposure to any dose of lebrikizumab (maternal report and confirmation with medical records) when available. First date from 5 half-lives (123 days) prior to the estimated date of conception through end of pregnancy.
No exposure to lebrikizumab during pregnancy	Comparator	Maternal report	No exposure to any dose of lebrikizumab from 5 half-lives (123 days) prior to the estimated date of conception or anytime during pregnancy.

Variable	Role	Data Source(s)	Operational Definition
Exposure to phototherapy, systemic therapy other than lebrikizumab, or both, or another IL-13–targeting biologic for the treatment of AD	Primary Comparator	Maternal report Medical record	Exposure to any dose of phototherapy, systemic therapy other than lebrikizumab, or both, or another IL-13–targeting biologic for the treatment of AD within 5 half-lives prior to the estimated date of conception or anytime during pregnancy
Unexposed to phototherapy or systemic therapy for the treatment of AD during the pregnancy period	Secondary Comparator	Maternal report Medical record	May or may not have received treatment for AD but who have not been exposed to any dose of phototherapy or systemic therapy for the treatment of AD within 5 half-lives prior to the estimated date of conception or anytime during pregnancy.
Major structural birth defect	Pregnancy outcome	Maternal report Medical record OTIS investigator review Dysmorphology evaluation	The registry adopts the term “major structural defect” (that is, birth defect) for an abnormality usually referred to as a “congenital abnormality” and defines major structural defect as follows: Any major structural or chromosomal defect defined and classified, using the CDC MACDP classification of birth defects (CDC 2023), including any intervention to correct the structural defect and its outcome, in any pregnancy including those ending in a live born infant or a pregnancy loss.

Variable	Role	Data Source(s)	Operational Definition
Minor structural defect	Infant outcome	Dysmorphology evaluation	A defect that occurs infrequently in the population but has neither cosmetic nor functional significance to the child and is identified using a study-related checklist (Appendix 2) incorporated into the study dysmorphology examination of live born infants.
Spontaneous abortion	Pregnancy outcome	Maternal report Medical record	Nondeliberate embryonic or fetal death that occurs prior to 20.0 weeks' gestation (CDC 2021a).
Stillbirth	Pregnancy outcome	Maternal report Medical record	A nondeliberate fetal death that occurs at or after 20.0 weeks' gestation but prior to delivery (Prager et al. 2021).
Elective termination/ abortion	Pregnancy outcome	Maternal report Medical record	A deliberate discontinuation of pregnancy through medication or surgical procedures. Reasons for elective termination/abortion are captured and are classified as due to medical reasons or nonmedical reasons.
Preterm delivery	Pregnancy outcome	Maternal report Medical record	A spontaneous or induced delivery at <37.0 gestational weeks, as counted from the first day of LMP, reported by the mother and validated through the medical record (CDC 2021b).
Small for gestational age	Infant outcome	Maternal report Medical record	Birth size (weight, length, or head circumference) <10th percentile for sex and gestational age using NCHS pediatric growth curves for full term infants. Prenatal growth curves specific to preterm infants are used for preterm infants (Olsen et al. 2010).

Variable	Role	Data Source(s)	Operational Definition
Small for age postnatal growth at 1 year of age	Infant outcome	Medical record	Postnatal size (weight, length or head circumference) <10th percentile for sex and age using NCHS pediatric growth curves and adjusted postnatal age for preterm infants.
Serious infection	Infant outcome	Maternal report Medical record	Defined as any infection requiring hospitalization identified in live born infants up to 1 year of age.
Developmental milestones	Infant outcome	Neurodevelop-mental questionnaires	Screening for achievement of neurodevelopmental milestones performed using the Ages and Stages Questionnaire (ASQ)-3 at 12 months of age. An abnormal score is defined in the scoring guidelines.
Neonatal death	Infant outcome	Maternal report Medical record	Death of a live born infant between delivery and 28 days of life.

Abbreviations: CDC = Centers for Disease Control and Prevention; LMP = last menstrual period; MACDP = Metropolitan Atlanta Congenital Defects Program; NCHS = National Center for Health Statistics; OTIS = Organization of Teratology Information Specialists.

9.3.4. Demographic and Clinical Characteristics

Potential confounders and other covariates to be collected include maternal age, race/ethnicity, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, medication, vaccine and vitamin/mineral exposures, and prenatal tests. Table 9.2 provides a description of corresponding variables to be included in this study. The SAP will provide greater detail on covariate definitions.

Table 9.2. Covariates, Role, and Source of Data

Variable	Role	Data Source(s)	Operational Definition
Maternal age (years)	Potential Confounder	Maternal report	Maternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34).
Paternal age (years)	Potential Confounder	Maternal report	Paternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34).
Maternal race	Potential Confounder	Maternal report	Maternal (White, Black, Asian/Pacific Islander, Native American, Other).
Maternal ethnicity	Potential Confounder	Maternal report	Maternal (Hispanic, Non-Hispanic).
Maternal education	Potential Confounder	Maternal report	Maternal Educational Category (years of completed education <12, 12-15, >15).
Socioeconomic category	Potential Confounder	Maternal report	Hollingshead Socioeconomic Category based on maternal and paternal occupation and education (1-5) (Hollingshead 1975)
Maternal height	Potential Confounder	Maternal report	Maternal height (cm).
Maternal prepregnancy body weight	Potential Confounder	Maternal report Medical record	Maternal prepregnancy body weight (kg) (confirm with medical record when available).
Maternal prepregnancy body mass index (BMI)	Potential Confounder	Maternal report	Maternal prepregnancy BMI (<18.5, 18.5-24.9, 25-29.9, ≥30).
Number of prior pregnancies	Potential Confounder	Maternal report Medical record	Number of times ever pregnant (1, 2-3, 4-5, ≥6) (confirm with medical record when available).
Previous live birth or stillbirth deliveries	Potential Confounder	Maternal report Medical record	Number of previous live birth or stillbirth deliveries (0, 1-2, 3-4, ≥5) (confirm with medical record when available).
Previous pregnancies ending in spontaneous abortion	Potential Confounder	Maternal report Medical record	Number of previous pregnancies ending in spontaneous abortion (0, 1, 2, ≥3) (confirm with medical record when available).

Variable	Role	Data Source(s)	Operational Definition
Previous pregnancies ending in elective termination/abortion	Potential Confounder	Maternal report Medical record	Number of previous pregnancies ending in elective termination (0, 1, 2, ≥3) (confirm with medical record when available).
Family history of a major structural birth defect	Potential Confounder	Maternal report Medical record	Yes/No.
Gestational age at enrollment	Potential Confounder	Maternal report Medical record	Weeks of pregnancy at time of enrollment, continuous and categorical (<13, 13-19.9, ≥20): gestational age is calculated from the first day of LMP.
Calendar year at estimated date of conception	Potential Confounder	Maternal report Medical record	Year of enrollment at estimated date of conception.
Referral source	Potential Confounder	Maternal report	Source options: Sponsor, OTIS service, Health care provider, Internet, Other, UC Rely.
Geographic area of residence	Potential Confounder	Maternal report	Geographic area of residence (that is, US, Canada).
Atopic dermatitis symptom/ severity measure	Descriptive Covariate	Maternal report	Disease symptom/severity measures using POEM (Charman et al. 2004).
Prenatal vitamin, Multivitamin, or Folic acid use in pregnancy	Confounder	Maternal report	Prenatal, multivitamin or Folic acid supplement use by timing (began prior to conception, postconception only, not taken at all).
Alcohol use in pregnancy	Confounder	Maternal report	Yes/No. Dose and frequency are captured.
Illicit drug use in pregnancy	Confounder	Maternal report	Yes/No. Drug type, dose, and frequency are captured.
Tobacco use in pregnancy	Confounder	Maternal report	Yes/No. Type of tobacco use, dose, and frequency are captured.
Prenatal diagnostic tests prior to enrollment	Stratification Covariate for Major Birth Defects	Maternal report Medical record	Tests performed prior to enrollment (Ultrasound Level 1, Ultrasound Level 2, Chorionic Villus Sampling, Amniocentesis).
Prenatal diagnostic tests anytime during pregnancy	Descriptive Covariate	Maternal report Medical record	Tests performed anytime in pregnancy (Ultrasound Level 1, Ultrasound Level 2, Chorionic Villus Sampling, Amniocentesis).

Variable	Role	Data Source(s)	Operational Definition
Current medication use	Confounder	Maternal report	Prescription and over-the-counter medications are captured for the period of time from the first day of LMP through the end of pregnancy. Dose, frequency, duration, and indication including stop and start dates are collected.
Years since diagnosis of approved indicated disease	Confounder	Maternal report Medical record	Years since diagnosis of approved indicated disease.
Comorbid maternal medical conditions	Confounder	Maternal report Medical record	Comorbid maternal medical conditions (for example, chronic hypertension, asthma).
Treatment history for the indicated disease	Confounder	Maternal report Medical record	Treatment history (drug, dose, duration) for the indicated disease with 2 years of LMP.
Pregnancy complications	Descriptive Covariate	Maternal report Medical record	Pregnancy complications, including preeclampsia and gestational diabetes.
Maternal pregnancy exposure to a known human teratogen	Confounder	Maternal report Medical record	Maternal pregnancy exposure to a known human teratogen (Appendix 3).

Abbreviations: LMP = last menstrual period; OTIS = Organization of Teratology Information Specialists; POEM = Patient Oriented Eczema Measure.

9.4. Data Sources

As part of the OTIS Pregnancy Registry protocol, data are collected using maternal interviews, medical record review (obstetric, delivery hospital, pediatric, other specialty provider if applicable, or a combination of the listed), the pregnancy exposure form, the ASQ, and study-related dysmorphology examinations of live born infants (see Table 9.3). For women with AD, the POEM (Charman et al. 2004) will be used to evaluate severity.

Medication or vaccine exposures are entered into the study database and are coded using the Slone Drug Dictionary. Major structural birth defects are coded using the MACDP coding list. This coding system will be used in all reports of major congenital malformations and the final report and final analysis.

For pregnancies ending in at least 1 live born infant, data will also be collected from the study-related dysmorphology examination conducted via telemedicine, from the 1-year pediatric medical record, and from the ASQ at approximately 1 year of age to assess developmental milestones.

The following data sources are considered the primary data sources for the study: maternal interviews, medical records, pregnancy exposure form, dysmorphology examination form, and

developmental milestones screening questionnaire data (ASQ-3). Data will be extracted from these sources and entered into a customized OTIS/MTB study database located in the research center and developed specifically for the OTIS/MTB Pregnancy Studies.

Table 9.3. Timing of Cohort Enrollment, Interviews, Examinations, and Medical Records

	Anytime in Pregnancy	20-22 Weeks' Gestation[a]	32-34 Weeks' Gestation[b]	0-6 Weeks Postdelivery	0-12 Months Postdelivery	1 Year Postdelivery
Referral[c]	√					
Enrollment and Consent[c]	√					
Enrollment Interview[c]	√					
Interim Interview I		√				
Interim Interview II			√			
Pregnancy Outcome Interview and Request for Medical Records				√		
Medical Record Review					√	
Dysmorphology Examination					√	
Ages and Stages Questionnaire (ASQ-3)					√	
Pediatric 1-Year Medical Records Request and Review						√

[a] If a participant is enrolled and intake interview is conducted after 18 weeks' gestation, only 1 interim interview will be conducted during pregnancy at 32 to 34 weeks' gestation.

[b] If a participant is enrolled and intake interview is conducted at 30 weeks' gestation or after, no interim interview will be collected.

[c] Women may enroll in the study anytime during pregnancy.

9.4.1. Modalities of Recruitment

All exposed and comparison individuals will be recruited through spontaneous contacts with participating OTIS member services in locations throughout US and Canada and through active recruitment strategies, for example, direct mailings to HCPs, website, and healthcare professional meetings in alignment with the OTIS Pregnancy Registry Protocol. Each OTIS service will provide exposure information in the routine manner for all exposed and unexposed women who initially make contact with the service with questions regarding a current pregnancy. Subsequently, each OTIS service will request permission to refer the participant to the research center at the UCSD. Potential participants who agree to be referred will contact the research center or be contacted if they prefer. Women can self-refer via the OTIS Pregnancy Registry website or toll-free telephone number (available in various sources including the product prescribing information), email, text, or chat. HCPs can also contact the OTIS Pregnancy Registry and refer patients; however, in all cases, the participant is the individual pregnant woman who provides informed consent for participation and completes the interview-based data collection.

The FDA website (https://www.fda.gov/consumers/pregnancy-exposure-registries/list-pregnancy-exposure-registries) lists the OTIS Pregnancy Registry and will have this registry added to the listing. The study will also be listed on ClinicalTrials.gov.

To reach a broad population and raise awareness about the study, OTIS Pregnancy Registry studies use direct to consumer social media. OTIS also has partnerships with agencies, such as the CDC, and professional societies, including the Society for Maternal Fetal Medicine and the American Academy of Allergy, Asthma, and Immunology, as well as patient organizations such as the National Eczema Association. Partners and members of the Scientific Advisory Board (see Section 13.1.1) promote the OTIS Pregnancy Registry network and studies on their websites and through presentations and exhibits at professional meetings. These strategies have resulted in cohort recruitment of a diverse sample including representation of women from each of the major race/ethnicity groups as well as across the range of socioeconomic status.

As OTIS Pregnancy Studies is conducting pregnancy registries for other AD products, each with a comparator group of pregnant women with AD; the methods employed to recruit participants for this study will be aided by existing efforts for other similar registries.

Once the target sample size is met for this study or the recruitment period has come to an end in 2033, whichever comes first (see Section 9.5), recruitment efforts for the study will cease, and study enrollment will be closed.

Retention of participants in the OTIS Pregnancy Registry is supported by frequent contact with the enrolled participant, building and maintaining a relationship between the study interviewer and the mother herself, and by ensuring the multiple alternative contact numbers/addresses are obtained and updated.

9.4.2. Participant Data

Below is a detailed description of each interview, the dysmorphology exam, and the developmental milestone screening questionnaire data (ASQ-3), as conducted under the OTIS Pregnancy Registry protocol.

9.4.2.1. Intake/Enrollment Interview

Following oral informed consent, a structured maternal intake telephone interview is conducted at enrollment by a trained research associate from the OTIS Research Center. This interview includes questions on the following: pregnancy history, number of live births, and multiple gestations; current health history; prepregnancy weight and height; socioeconomic and demographic information, including maternal and paternal occupation, education, and ethnicity; income category; current medication use, both prescription and over the counter; other environmental or occupational exposures; alcohol, tobacco, caffeine, and illicit drug use; vaccine exposure prior to and during pregnancy; current pregnancy complications including illnesses; family history of adverse pregnancy outcomes, including major structural birth defects and genetic disorders; and names and addresses of health care providers. To supplement future interviews and improve recall, participants are given a pregnancy exposure form to record any additional exposures (medications, vaccinations, vitamins, and so on) or events as the pregnancy progresses. Women will be asked to respond to a severity assessment questionnaire (POEM) to provide a means of assessing comparability of disease severity between the cohorts. Each woman is also sent the informed consent document and the US HIPAA (HHS 2013) Authorization Addendum, when applicable, via electronic signature or paper, and a research HIPAA compliant obstetric medical record release form.

9.4.2.2. Interim Interviews I and II

Telephone interviews are conducted at 20 to 22 and 32 to 34 weeks' gestation, if enrolled before those gestational weeks, by a trained research associate from the OTIS Research Center. Women who have enrolled prior to 18 weeks post-LMP will be interviewed by telephone at 20 to 22 weeks post-LMP, 32 to 34 weeks post-LMP, and within 0 to 6 weeks after the expected due date. Women who have enrolled between 19 and 30 weeks post-LMP will be interviewed at 32 to 34 weeks post-LMP (see Table 9.3). These interviews are intended to update records of pregnancy exposures (medications, vaccinations, vitamins, and so on); results of prenatal tests; events of interest since last interview, including if the pregnancy has ended prior to the expected due date; and contact information, as well as administration of the POEM.

9.4.2.3. Pregnancy Outcome Interview

At any of the interim interview points, if the pregnancy has ended, the outcome interview will be conducted at this time or at the earliest convenient time for the mother. For women who are still pregnant at the 32 to 34 week interview, the outcome interview will be conducted within 0 to 6 weeks after the expected due date.

- For women with live born infants: a structured telephone interview and information will be elicited on the following: date of delivery, hospital location and mode of delivery; sex, birth weight, length and head circumference; Apgar scores; description of delivery or birth complications including malformations; type and length of hospital stay for mother and infant; delivering physician's and infant physician's names and addresses; method of infant feeding; pregnancy weight gain; and additional exposures and results of prenatal tests occurring since the previous interview.
- For women with pregnancy ending in SAB or elective termination: information will be elicited on the following: date and type of outcome, hospital location if applicable, prenatal diagnosis, pathology results if available, and additional exposures and results of prenatal tests occurring since the previous interviews.
- For women with a stillborn infant: the interview will include all of the information for SABs or elective terminations plus information on sex, birth size, and autopsy results if available.

9.4.2.4. Medical Records and General Pediatric Evaluation

Upon completion of the outcome interview, each participant will be mailed a packet electronically or by hard copy mail containing research HIPAA compliant medical records release forms for the delivery hospital, obstetrician, pediatrician, and specialty physician, if applicable. For women whose pregnancies have ended in SAB, elective termination, or stillbirth, records release forms will be mailed for the specialist's evaluation, if applicable, and if prenatal diagnosis, pathology, or autopsy reports are available. Each participant will be asked to sign (electronically or wet signature) the medical records release forms, as well as UCSD HIPAA Authorization Addendum, if they or their child receives medical care at UCSD/Rady Children's Hospital, and to return these authorization documents along with the pregnancy exposure diary form.

Upon receipt of the signed medical records release forms, a standard physical evaluation form will be mailed to each pediatrician or other physician responsible for the care of each live born infant. This form includes information on infant size at the time of the latest examination and an open-ended question about postnatal complications and major structural defects.

At 1 year of age, another research HIPAA compliant medical records release form for the pediatrician or HCP caring for the child will be sent to the participant for signature. The signed form with a standard physical evaluation form will be sent to the HCP to request updated information on growth, and major structural defects.

9.4.2.5. Dysmorphology Evaluation

Pregnancies resulting in live born infants in each cohort, and who agree to the exam, will be eligible for an examination by one of a team of study-dedicated dysmorphologists. The team is made up of pediatric HCPs with subspecialty fellowship training in dysmorphology/genetics. The physical examinations evaluate infants for both major and minor structural defects and provide increased sensitivity for detecting a specific pattern of malformation should one exist.

Infants will be examined within the first year of life or as soon as the examination can be practically arranged. Examinations will take place via a telehealth visit.

Infant examinations will be conducted using a standard checklist of minor malformations on a standard physical evaluation form. In addition, with signed parental consent, when the mother agrees, a recorded video of the infant will be taken to aid in validating any findings across examiners.

Dysmorphologists will perform these examinations blinded to the exposure or comparison group status of the mothers. Participants are asked to sign an examination consent via electronic consent prior to telehealth exams. If deemed necessary, the examiners will meet to review video of children to assess any patterns that may be identified.

9.4.2.6. Developmental Milestones

When the child is approximately 12 months of age, adjusted for premature delivery, the mother will be asked to complete the ASQ-3 developmental milestones screening questionnaire (Squires et al. 2009).

9.4.2.7. Procedure and Consequences of Participant Withdrawal

As stated in the informed consent, any study participant may withdraw from the study at any time for any reason; however, data that have been collected up to the time of withdrawal may be used. Participants who withdraw from the study after the collection of birth or end of pregnancy outcome will not be considered lost-to-follow-up. Participants who withdraw from the study prior to the collection of birth or end of pregnancy outcome will be considered lost-to-follow-up, and the SAP addresses the method whereby these data will be addressed.

9.5. Study Size

The proposed sample size is 500 women recruited over an 8-year period: 100 women enrolled in the exposed cohort, 200 women enrolled into the primary comparator group, and 200 women enrolled into the secondary comparator group. Up to an additional 50 women may be enrolled in the Exposure Series group.

Based on previous experience with the OTIS Pregnancy Registry, it is estimated that women will be an average of 7 to 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% (Chambers et al. 2016). This will result in known outcomes for approximately 95 pregnancies in Cohort 1 and 190 pregnancies in each of the comparison group, including 80 pregnancies with at least 1 live born infant in Cohort 1 and 160 in each of the comparison groups at the end of recruitment.

Baseline rates of major structural birth defects, specific patterns of 3 or more minor structural defects, premature delivery, and SGA are based on previous MTB/OTIS studies and on general population data. Rates of SAB in the general population are 15% to 20% (Avalos et al. 2012; Magnus et al. 2019). However, because women do not typically enroll in pregnancy registries until after 7 to 8 weeks' gestation when the highest risk of SAB has passed, the baseline estimate

is drawn from previous OTIS studies. Table 9.4 gives the minimum detectable effect sizes with 80% power (2-sided significance level 0.05, except as noted below for pattern of minor structural defects), for the comparisons described above. The current sample size provides 80% power to detect a RR of approximately 4.4 or greater in major structural defects among pregnancies ending in at least 1 live birth compared to the baseline prevalence of 3% in the comparison groups. This is consistent with the population prevalence of major structural defects of 2.8% in the Atlanta metropolitan area (CDC 2023).

Table 9.4. Sample Size and Detectable Effect Size with Power for Comparison of Exposed Cohort 1 to Unexposed Cohort 2

Endpoint	N in the Exposed Cohort	N in the Unexposed cohort	Baseline Rate or Standard Deviation in Disease-Matched Group	Relative Risk	Power[a]
Major structural defects[b]	80	160	3.0% (CDC 2023)	4.4	80%
Specific pattern of 3 or more minor structural defects[c]	80	160	1.0% (Leppig et al. 1987)	7.0	71%[d]
Spontaneous abortion/still birth	90	180	10.0% (Avalos et al. 2012)	2.4	80%
Preterm delivery	80	160	10.0% (Ferré et al. 2016)	2.5	80%
Small for gestational age	80	160	10.0% (Nellhaus 1968; Olsen et al. 2010; CDC 2023)	2.5	80%

Abbreviations: CDC = Centers for Disease Control and Prevention; N = number of participants.

[a] All tests are 2-sided with alpha = 0.05, based on Fisher's exact test unless specified otherwise. Calculations conducted using R.

[b] Primary endpoint; among live births.

[c] One-sided.

[d] Consistent with known teratogens, a 5% to 10% incidence (that is, 4 to 8 infants) with a specific pattern of minor defects in the exposed group would be considered meaningful. However, for purposes of calculating a RR, an incidence of a specific pattern of 3 or more minor structural defects in the comparison group is set at 1.0%, resulting in a power to detect the relevant effect size of somewhat less than 80%.

9.6. Data Management

Participant data are recorded on data forms. Investigators and study personnel are responsible for the integrity of the data (that is, accuracy, completeness, legibility, and timeliness) that is included in the study reports and data analyses.

The OTIS Pregnancy Registry research coordinating center will keep all records, including the identity of all participating women, all original signed consent to release information, copies of interview and pregnancy exposure forms, SAE forms, source documents, and adequate documentation of relevant correspondence. The records will be retained by the investigator by the longer of applicable law or as required by their records retention schedule.

As per the OTIS Pregnancy Registry protocol, data are collected using maternal interview, medical record, the dysmorphology exam, ASQ-3 electronic form, and the pregnancy exposure form. Maternal interview data are recorded on hard copies of forms, and these forms will be retained by OTIS. These forms are considered the primary data sources for the registry. Medical records, medical record abstraction forms, and ASQ-3 are hard copies or electronic copies and are retained on a secure server or in locked files. Data from maternal interview and medical record abstraction forms are extracted and entered into a customized OTIS registry database located in the research center and developed specifically for the OTIS Pregnancy Research Studies. Hard copies of participant files and written signed consent forms will be kept in a locked cabinet under the supervision of the study investigators. Data collection and validation procedures will be detailed in appropriate operational documents.

The database itself has built in range limits for key variables that prevent certain data entry errors. In addition, all data entry forms will be reviewed for logical errors by the study data manager on a regular basis and 100% of key variables are double-checked for data entry accuracy. The registry statistician will also conduct reviews of the cumulative data from the study in the database for distributions and values that are illogical. The registry manager will be responsible for working with the data manager and the supervisory staff to oversee the data validation procedures.

Access to the database is controlled by password, with different access privileges assigned to the managers, interviewers and data entry staff, and administrative staff; these privileges are outlined in detail in the OTIS Data Management Guide, Data Entry Standard Operating Procedure, and supplements to these guides. An audit log is built into the database to archive all such entry edits.

Hard copies of participant files and participant-written, signed consent forms are kept in locked cabinets in locked file rooms or electronically secured files under the supervision of the study investigators.

9.7. Data Analysis

All analyses will be performed by the OTIS Research Center according to a prespecified and approved SAP.

9.7.1. Analysis Software

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

9.7.2. Analysis Variables

9.7.2.1. Outcome Classification for the Primary Outcome – Major Structural Defects

The method for classifying major structural defects for purpose of analysis has been described by the study investigators and the OTIS Research Group (Chambers et al. 2001; CDC 2023) and has been used in previous studies conducted by OTIS.

9.7.2.2. Inclusion Criteria for the Primary Outcome – Major Structural Defects

Definition: a major structural defect is defined as a defect that has either cosmetic or functional significance to the child (for example, a cleft lip).

- ***Classification of major structural birth defects*** will be performed according to the CDC coding list (CDC 2023) and applied equally across all cohorts in the study. Some major structural birth defects are known consequences of pregnancy events, such as premature delivery, and are therefore not directly due to drug exposure. For example, isolated patent ductus arteriosus or isolated inguinal hernia in an infant delivered before 36 weeks' gestation are considered consequences of prematurity, and therefore, using CDC coding criteria, none of these defects are counted as major structural defects. Other structural defects, such as club foot or cranial synostosis, could be due to position of the infant in the uterus or could be primary defects initiated earlier in pregnancy. In most cases, it is not possible to know the true onset or etiology of the defect. Therefore, using CDC coding criteria, these anomalies are counted as major structural defects uniformly across all cohorts.
- Using CDC coding criteria, chromosomal anomalies are counted as major structural birth defects. Although it is unlikely that a drug exposure could cause a chromosomal defect, it is not impossible. These major structural defects are counted uniformly across all cohorts in the study. Similarly defects that are identified as due to genetic syndromes are coded uniformly across all cohorts.

This uniform coding reduces differences in outcome definitions between studies for a better interpretation of results in the event they are compared. Further, it allows for the use of the external comparator group compiled by the MACDP. It is anticipated that the occurrence of defects that are unrelated to drug exposure in the proposed study population will be nondifferential across cohorts. Therefore, their inclusion, when indicated, represents part of the baseline risk for major structural defects in each cohort. This should not impact the risk estimates and measures of association.

However, for the primary analysis of major structural defects, chromosomal anomalies will be excluded. In sensitivity analysis, they will be included, as outlined in the SAP.

- For the primary outcome of major structural defects, the etiologically relevant window, with rare exceptions, is any exposure in the first trimester of pregnancy. Therefore, the analysis subset in Cohort 1 will be restricted to those with exposure to at least 1 dose of lebrikizumab from 5 half-lives (123 days) prior to the estimated date of conception through the end of the first trimester. It is possible that some pregnant women in Cohort 1 could have exposure to lebrikizumab limited to the second or third trimester, and these would be considered separately. Duration and gestational timing of exposure to lebrikizumab will also be considered.
- ***Time period for identification:*** major structural defects identified up to 1 year of age by the mother or the HCP/medical record will be included in the primary analysis. Defects identified after that time frame will be described and considered separately.
- ***Confirmation of defects:*** independent confirmation of certain defects will be required. For example, a heart murmur thought to represent a ventricular septal defect prior to 1 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 noted will be included as occult spinal dysraphism only if confirmed by appropriate imaging studies.
- ***Adjudication of major structural birth defects:*** major structural birth defects when reported are first classified by the OTIS study manager once all efforts have been made to obtain adequate information from the mother and infant's HCPs. All major structural birth defects are then reviewed in detail by the coinvestigator on this study who is an expert in birth defects. The coinvestigator is always blinded to the pregnancy exposure group at the time of the evaluation. If there is a discrepancy in the classification based on these 2 independent reviews, additional consultation is required for adjudication or classification. This is performed by a member of the Scientific Advisory Board. These consultants are also blinded to exposure information at the time of the classification review. After this classification has been completed, at each annual interim and the final Scientific Advisory Board meeting for the study, all major structural birth defects are reviewed. The members of the Scientific Advisory Board, who are experts in major structural birth defects, as part of the review process, may ask for additional information regarding classification of major structural birth defects. However, at the time of the annual report review, the Scientific Advisory Board members are not blinded to exposure. The final adjudication of the classification of major structural defects is made through this multi-step process and all data presentations derived from the study will clearly describe the adjudication process.

9.7.2.3. Exclusion Criteria for the Primary Outcome – Major Structural Defects

Defects will be excluded based on criteria outlined in the CDC coding list as outlined in Section 9.7.2.2.

- ***Time period for identification:*** structural defects ascertained after 12 months of age will not be included in the primary analysis but will be considered separately in the context of a possible pattern.
- ***Defects identified in SABs/miscarriage, stillbirths, or elective terminations/abortions****:* defects identified by prenatal ultrasound or examination of the products of conception following elective or SAB/miscarriage or stillbirth will not be included in the primary analysis of the primary outcome due to potential bias involved in nonuniform use of prenatal diagnosis and pathology evaluation for all abortuses; however, these defects will be included in the additional analysis of the primary outcome that includes all defects in the numerator over all pregnancies enrolled in the prospective cohort with known outcome in the denominator (excluding lost-to-follow-up).

9.7.2.4. Outcome Classification for Secondary Outcomes

- ***SAB:*** SAB/miscarriage is defined as nondeliberate fetal death that occurs prior to 20.0 weeks post-LMP. The analysis subset for the secondary outcome of SAB will be restricted in Cohort 1 to those who were exposed to any dose from 5 half-lives (123 days) prior to the estimated date of conception to prior to 20 weeks' gestation and enrolled prior to 20.0 weeks' gestation. The analysis subset for Cohorts 2 and 3 will be restricted to those who enrolled prior to 20.0 weeks' gestation.
- ***Stillbirth****:* stillbirth is defined as nondeliberate fetal death anytime in gestation at or after 20 weeks post-LMP.
- ***Elective termination:*** elective termination/abortion is defined as deliberate termination of pregnancy at any time in gestation. Reasons for elective abortions are captured and are classified as due to medical reasons or non-medical reasons.
- ***Premature delivery:*** premature delivery is defined as live birth prior to 37.0 weeks' gestation as counted from LMP or calculated from first-trimester ultrasound-derived due date if LMP uncertain or more than 1-week discrepant. The analysis subset for the secondary outcome of premature delivery will be restricted in Cohort 1 to those who were exposed to any dose from 5 half-lives (123 days) prior to the date of conception to prior to 37 weeks' gestation and enrolled prior to 37.0 weeks' gestation. The analysis subset for Cohorts 2 and 3 will be restricted to those who enrolled prior to 37.0 weeks' gestation.
- ***SGA:*** SGA is defined as birth size (weight, length or head circumference) less than the 10th percentile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm infants (CDC 2000; Olsen et al. 2010).

- ***Minor structural birth defects*:** a minor structural birth defect is defined as a defect that has neither cosmetic nor functional significance to the child (for example, complete 2,3 syndactyly of the toes). Minor structural defects will be identified only through the study dysmorphology examination for live born infants using the study-specific checklist. The exposure of interest is 5 half-lives (123 days) prior to the estimated date of conception to the end of the first trimester.
- ***Postnatal growth deficiency:*** postnatal growth deficiency is defined as postnatal size (weight, length or head circumference) less than the 10th percentile for sex and age using National Center for Health Statistics pediatric growth curves and adjusted postnatal age for premature infants if the postnatal measurement is obtained at less than 1 year of age (CDC 2000).
- ***Developmental milestones:*** 1 or more domains scored as abnormal on the ASQ-3 completed by the mother when the infant is approximately 12 months of age will define achievement of developmental milestones.
- ***Serious infections:*** serious infections are defined as any infection requiring hospitalization identified in live born infants up to 1 year of age.
- ***Neonatal death:*** defined as death of live born infant within 28 days of delivery.

9.7.2.5. Lost-to-Follow-Up

Participants 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 minimum of 13 telephone attempts and attempt to contact by mail as per study procedure manual within 1 year of the mother's estimated due date.

9.7.3. Statistical Methods

An interim report will be provided annually to Lilly containing descriptive data only on characteristics of women enrolled in the study and cumulative study outcomes. No statistical comparisons are planned for the annual interim reports. The final report will be provided to Lilly after closure of the study and is further detailed in the SAP.

9.7.3.1. Analysis of the Primary Outcome

The primary outcome of interest, that is, major structural birth defects, will be estimated in each cohort as a proportion, and its 95% CI, using 2 denominators: i) pregnancies ending in at least 1 live born infant and ii) pregnancies ending in at least 1 live born infant, stillborn, SAB, or elective termination. Data will also be presented by gestational timing of exposure.

For the primary endpoint, the exposure of interest is at least 1 dose of lebrikizumab at any time from 5 half-lives (123 days) prior to the estimated date of conception to the end of the first trimester, whether or not there is continued exposure to lebrikizumab in the second or third trimesters. The primary comparison will be the proportion of major structural birth defects between the lebrikizumab-exposed group and Comparator Group 1 (Diseased Comparator I – Phototherapy or Systemic Treatment) among pregnancies resulting in at least 1 live born infant.

A point estimate of the crude (that is, unadjusted) RR of the lebrikizumab-exposed group versus Comparator Group 1, as well as its 95% CI, will be computed.

The same analysis will be repeated using the second numerator and denominator encompassing pregnancies ending in at least 1 live birth, stillbirth, SAB, or elective termination but excluding those lost-to-follow-up.

Because women can enter the study at arbitrary times in gestation, participants are not followed from gestational age zero. Women with early end of pregnancy tend not to be captured in the study; this is referred to as left truncation in the literature and it leads to selection bias. To correct for this bias, confounder selection as well as PS estimation, to be elaborated later, will be performed using inverse probability of truncation and censoring weighting. Refer to the SAP for details.

Due to the observational nature of the study, the crude estimate of RR will be further adjusted for potential confounders (Rosenbaum 2002), provided that there are sufficient number of events available for analysis. A list of potential confounders will be provided in a separate table for each outcome prior to the final analysis. In addition, all of the following 3 criteria will be applied in accordance with the definition of confounders (Greenland et al. 1999; Xu et al. 2018): 1) by assessing each considered variable in a logistic regression model containing the exposure variable and the outcome variable to determine if inclusion of that single covariate changes the estimate of the odds ratio for exposure by 10% or more; 2) standardized mean differences greater than 0.1; and 3) association with the outcome with p-value less than 0.2 in the unexposed cohort, from the Wald test using the robust sandwich variance estimate for a logistic regression of the outcome variable on the covariate.

The confounders identified above will be used to build the PS for exposure (Rosenbaum 2002). R package “twang” or similar R package available at the time of analysis will be used for this purpose, following which standardized mean differences will be used to check the balance of the covariates between the cohorts.

The primary analysis will be performed with inverse probability of treatment weighting using the PS to estimate the causal RR. In the inverse probability of treatment weighting approach, stabilized weights that are further truncated to be between 0.1 and 10 will be used, if necessary (Austin and Stuart 2015). The bootstrap variance estimator will be used following the inverse probability of treatment weighting approach to derive the 95% CIs. Refer to the SAP for details.

A secondary analysis will be conducted using outcome regression, that is, a logistic regression model will be fitted with major structural defect (Y) as outcome and exposure (A) and PS (L) as regressors, with the truncation weights. Standardization will be performed to obtain the estimated causal RR (Hernán and Robins 2020). The CIs are obtained by bootstrap. Refer to the SAP for details. As a secondary approach, following Levenson and Yue (2013), all potential confounders will be accounted for in the PS model.

Several sensitivity analyses will be performed for the primary outcome of major structural birth defects:

- One analysis will include chromosomal anomalies.
- Because AD disease severity measured in pregnancy is not a baseline covariate, that is, is not measured prior to treatment for AD, and can be influenced by AD treatment in pregnancy, the POEM score is not considered the measure of AD disease severity in this study to qualify as a true confounder. Therefore, in the primary analysis, the POEM score will not be considered a potential confounder. However, in a sensitivity analysis, it will determined if the effect estimate of exposure to lebrikizumab differs with inclusion in the model of the POEM score captured at the time of enrollment and at a gestational timing relevant to the outcome of interest (for example, first trimester for major birth defects).
- In addition, sensitivity analyses for the analysis of major and minor structural birth defects will be conducted restricting the sample in Cohort 1 to those exposed to at least 1 dose from the estimated date of conception through the end of the first trimester.
- A graphical presentation of the gestational timing of exposure to lebrikizumab will be presented for those cases in Cohort 1 that end in a major structural birth defect.
- Exposure to a known human teratogen (Appendix 3) is included in the list of potential confounders for Cohort 1 versus Comparison Group 1 and 2. However, in the case where there are insufficient numbers of events to consider regression adjustment, a sensitivity analysis will be performed excluding women with exposure to known teratogens in the three cohorts to address this potential confounder.
- As prior knowledge from prenatal ultrasound or diagnostic testing could introduce bias, a sensitivity analysis for the primary outcome of major structural birth defects will be performed stratified on prenatal testing prior to enrollment (yes/no).
- A sensitivity analysis is also planned stratified on any abnormal finding on prenatal ultrasound or diagnostic testing prior to enrollment (yes/no). These analyses are described in detail in the SAP.

9.7.3.2. Analysis of the Secondary Outcomes

The analysis of SAB and stillbirth: Only those participants who are enrolled prior to 20 weeks of gestation are eligible for the analysis of SAB. Because they are not followed from gestational age zero, survival analysis methods will be used to handle left truncation, under the assumption that the truncation time and event time are (conditionally) independent, 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 and Chappell 1998). The Cox proportional hazards regression models incorporating left truncation will be used to estimate the hazard ratio of

different cohorts, as well as to obtain the 95% CIs. Stillbirth will be analyzed in a similar fashion. To account for potential confounding, PS methods described above will be applied, where regression adjustment will be used with the Cox model to obtain the adjusted hazard ratio.

The analysis of premature delivery: Only those pregnancies that are enrolled prior to 37.0 weeks of gestation and result in a singleton live birth in all cohorts, and enrolled and exposed prior to 37.0 weeks in the exposed cohort are eligible for the analysis of premature delivery. These data will be analyzed similarly to SAB, as described above, using survival analysis methods to handle possible right-censoring.

The following will be considered binary endpoints: SGA at birth in weight, height, and head circumference, respectively, and growth deficiency at about 1 year of age in weight, height, and head circumference, respectively. 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.

Multiple births will be included in the analyses of minor structural defects, neonatal death, developmental milestones in live born children at 12 months of age, and serious infections. These outcome variables will thus likely contain correlated data due to twins or higher order multiples, and the generalized estimating equations approach will be used (Liang and Zeger 1986; Diggle et al. 2002).

9.7.3.3. Missing Data

Missing values for covariates typically occur in less than 5% of the cases for any single covariate. They are assumed to be missing at random. When there are missing values in any of the selected confounders, multiple imputation will be conducted, using the R package multivariate imputation by chained equations (van Buuren and Groothuis-Oudshoorn 2011), as appropriate depending on level of missingness. Multiple imputation will be conducted for missing data using the entire dataset, that is, on all cohorts combined.

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 multiple imputation (Pan 2000). An exact SAB time will be imputed by sampling uniformly from the corresponding time window.

9.7.4. Evaluation for a Pattern of Major and Minor Structural Defects

The following steps will be taken to evaluate any pattern of major structural defects as described in Chambers et al. 2001:

- A review of major structural defects will be made by category. A review of specific major structural defects will be conducted, taking into consideration timing, dose, and biological plausibility.
- Major structural defects identified in aborted fetuses will be reviewed separately from the primary analysis for the live born infants.

- Among infants with 3 or more minor structural defects, the lebrikizumab-exposed group will be examined for evidence of a specific pattern of 3 or more minor structural defects in any 2 or more children. If such a pattern is identified, Comparator Groups 1 and 2 will be evaluated for any evidence of the same pattern. (Chambers et al. 2001).

9.7.5. Annual Analysis and Termination of the Study

OTIS will develop an annual reports and any additional ad hoc reports for evaluation by the Scientific Advisory Board members. Each report will be a composite of the cumulative data to date and will supersede any previous reports. Descriptive analyses will be presented, but no formal interim statistical analysis is planned. Each annual report and the final report for the Registry will provide a summary of the literature regarding lebrikizumab exposure and pregnancy outcomes. These annual reports will be provided to Lilly. At the end of the fourth year of the registry, an assessment of participant accrual will be conducted to determine the feasibility of continuing the pregnancy registry. The final analysis will be conducted when the cohort study has been completed. The study may be terminated at any time based on a variety of considerations. A recommendation regarding study progress and continuation will be made upon review by the Scientific Advisory Board (Section 13.1.1) and will be provided annually to Lilly.

9.8. Quality Control

Data used in this study are collected as part of the existing OTIS Pregnancy Registry protocol, which includes established quality control practices. Interview and examination data will be recorded on hard copies of forms, and medical records, medical record abstraction forms, and ASQ data will be electronic or hard copies of forms. These records and forms will be retained at the research center. Data from these forms will be extracted and entered into a customized database located at the research center. The data will be extracted and entered by trained study personnel with extensive experience with this type of information. Entries will be periodically reviewed for logical errors, and a random subset of intake and outcome forms will be double-checked for data entry accuracy. The method and duration of storage of data is addressed in the informed consent that each participant will agree to in order to receive medical record information.

Access to the database will be controlled by password. Hard copies of participant files and signed consent forms will be kept in a locked cabinet under the supervision of the study investigators.

The data will be entered by trained study personnel with extensive experience with this type of information. Data will be collected and entered into the database according to the standard operating procedures for data collection and data entry established for this study.

The data manager will calculate monthly error rates for each data entry staff person and for the study overall and will recommend and initiate training/retraining where quality standards are not being met. The study manager will oversee this process and verify that training standards are achieved.

For the study endpoint of major structural birth defects, verification of the outcome identified and classification is performed on a monthly basis and is provided by blinded review by a study expert in birth defects.

9.9. Limitations of the Research Methods

This study will use data from the well-established OTIS Pregnancy Registry, which collects detailed data on prenatal/birth exposures, including timing of exposures during pregnancy, and outcomes. The primary limitation of this cohort study utilizing volunteer participants is potential selection bias in that women who agree to enroll in the study may represent particularly high- or low-risk pregnancies (Johnson et al. 2001); therefore, the study results will be strictly generalizable to only people fitting the profile of the sample of women who enroll. The use of inverse probability weighting to account for differences between the exposure and comparator cohorts will address these concerns to some extent. The data analysis stratifying on use of prenatal testing and on gestational timing of enrollment will also help control for confounding introduced by potential selection bias.

Another limitation of the study design relates to the evaluation of the incidence of SAB. Incidence rates of early SAB, that is, at 7 to 9 weeks post-LMP or less, will not be measured in a study that enrolls women after recognition of pregnancy. Therefore, SAB will be defined as late first-trimester and early second-trimester pregnancy loss. Analysis of SAB will be restricted to those who enroll prior to 20 weeks' gestation. In addition, if a high proportion of women enroll later in pregnancy, other survival biases may be introduced. A sensitivity analysis by gestational age at enrollment will be performed in order to address these questions. Analyses will be stratified by gestational age at enrollment to help address the potential selection bias.

Because early prenatal testing is so prevalent in the US and Canada, it may be difficult to achieve adequate numbers of participants if all pregnancies with prior prenatal testing are excluded from the analysis. Therefore, the study will include pregnancies enrolled prior to outcome but after a prenatal test has been performed as long as the test does not indicate the presence of a major structural defect. The FDA guidance document (FDA 2019) acknowledges that such an approach may be necessary to accrue adequate numbers. However, this practice could potentially bias the results by lowering the overall estimate of the prevalence of birth defects (Honein et al. 1999). The data analysis will address this in each annual and the final study report, as described in sensitivity analyses above, by stratifying on use of prenatal diagnostic testing prior to prenatal testing.

The calculation of frequency of major structural birth defects excludes fetal losses (SABs, elective terminations, or fetal deaths) for which no birth defects have been detected because they may introduce a classification bias. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or pregnancies with major structural birth defects. The study attempts to obtain information on major structural birth defects detected at the time of the outcome. However, the malformation status of the aborted fetus may not be known. For this reason, the primary comparison for this outcome of the study will be conducted among

pregnancies ending in live birth, and a secondary analysis of this outcome will include all pregnancies with known outcome.

It is expected that some exposures to lebrikizumab will occur in unintended pregnancies as more than half of all pregnancies in the US are unintended (Henshaw 1998). Therefore, the possibility of confounding by age, race, and other relevant demographic variables will be considered. For example, the rate of unintended pregnancies is higher among low income women/families than among other socioeconomic groups. It is possible that demographic variables will be associated with treatment exposure as well. As such, these factors will be taken into consideration in the recruitment of comparison groups and in the analysis.

It is not possible to predict the number of pregnancy exposures that will occur for a newly marketed medication, and therefore, sample size is based on estimates that may require revision as the study progresses. All possible measures will be taken to ensure registry awareness and outreach including marketing via websites, social media, print media, scientific conferences, and so on. Pregnancy registry enrollment rates are subject to drug utilization among pregnant women. Drugs with relatively low use among pregnant women (at most 20/100,000 live birth pregnancies) had less successful enrollment in pregnancy registries (Bird et al. 2018).

Another factor to be considered is the potential impact of changing trends in prescribing practices along with physician and maternal attitudes toward the use of lebrikizumab in pregnancy. For example, as more pregnancy outcome information becomes available, the length of exposure to lebrikizumab in study participants may change. These trends will need to be addressed in the analysis.

The primary comparator group is expected to be most comparable to the lebrikizumab-exposed women because it includes women treated with phototherapy or systemic therapy for the AD. The secondary comparator group includes women with AD who may or may not receive nonsystemic therapy for the treatment of AD within 5 half-lives prior to LMP and may include women with less severe AD than the lebrikizumab-exposed women and therefore potentially less comparable. It is also possible that women in the lebrikizumab-exposed group will enroll earlier in pregnancy than either of the comparator groups. The study will monitor disease severity and gestational age at enrollment and discuss any modifications needed in recruitment strategies as the study progresses.

Although all possible efforts will be made to retain women in the registry or follow-up with their HCPs, some women will be lost during follow-up. It could be possible that women lost during follow-up and with missing data on outcomes may be different compared to those with complete follow-up data. In previous OTIS studies, lost-to-follow-up rates have been low, typically less than 5% (Chambers et al. 2016). However, the characteristics of women lost to follow-up will be compared to those who are retained in order to understand the direction and magnitude of the bias due to lost-to-follow-up.

The study design has relative strengths with respect to the control of a large number of potential confounders. Information will be collected repeatedly throughout pregnancy on a variety of factors that may be related to exposure and to pregnancy outcome, and the use of a disease-

matched comparator group addresses to some extent the issue of confounding by indication. Misclassification bias due to poor recall is thought to be reduced in prospective study designs such as this one. In addition, each participant is interviewed at several predetermined intervals during pregnancy. Another strength of the study design is the anticipated minimal lost-to-follow-up rate. Based on previous experience of the investigators in the OTIS Pregnancy Studies, and the frequent study participant contact, lost-to-follow-up is expected to be less than 5% and therefore not expected to pose a threat to the validity of study results.

Finally, the primary strength of the cohort study portion of the registry is its sensitivity for detection of a pattern of malformation. As known teratogens are associated with specific patterns of malformation, this study design, by virtue of providing dysmorphological evaluation of prospectively ascertained and exposed infants, has the unique capability of detecting within reasonable limits such a pattern if it exists. The investigators and the Scientific Advisory Board's expert review and comment on the data and the inclusion of evaluation of a pattern of major anomalies are strengths.

9.10. Other Aspects

Not applicable.

10. Protection of Human Subjects

This observational study will be submitted to the IRB at UCSD, which oversees OTIS Pregnancy Studies for approval. Current documentation of ongoing IRB approval will be provided to the sponsor. Progress reports will be submitted to IRB as required.

This study will be conducted in accordance with applicable laws and regulations of the region, country, or countries where the study is being conducted, as appropriate.

10.1. Participant Information

The registry will ensure protection of participant personal data and will not include participant names on any reports, publications, or in any other disclosures, except where required by law.

10.2. Participant Consent

The informed consent form will be in compliance with UCSD regulatory requirements.

The informed consent forms used in this study, and any changes made during the course of the study, must be prospectively approved by the UCSD IRB before use.

The registry staff ensures that each study participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The registry will obtain informed consent from each participant or participant's legally acceptable representative before any study-specific activity is performed. The pregnant woman must agree to the oral consent form at the time of enrollment and before completing the intake interview. She must also sign for release of medical information and the HIPAA authorization, if applicable, to allow the registry to obtain information on the pregnancy and the pregnancy outcome from the participant's obstetric HCP, the hospital of delivery, and any healthcare specialist for treatment of the indicated disease and for the infant from the infant's pediatric HCP. The original oral and signed written informed consent documents and HIPAA authorizations will be maintained by the registry office. The original medical record release documents will be retained at the registry office as well, and copies will be sent to the institution or physician from whom records are being requested. These medical release documents are in the authorized format required by UCSD and are compliant with HIPAA regulations.

10.2.1. Participant Withdrawal

Participants may withdraw from the study at any time at their own request for any reason without prejudice to their future medical care by the physician or at the institution. Participants may also be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. In any circumstance, every effort will be made to document study participant outcome, if possible. The registry routinely inquires and records the reason for withdrawal. If the participant withdraws from the study, no further data will be collected, but the registry will retain and continue to use any data collected prior to the withdrawal of consent.

10.3. Institutional Review Board

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (for example, informed consent forms) by the IRB at the UCSD. The chairperson or the recording secretary of the IRB will provide documentation indicating approval. All correspondence with the IRB will be retained.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor, and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practice (Public Policy Committee and International Society for Pharmacoepidemiology 2015), in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association 2013) and HIPAA (Andrews et al. 1996; NIH 2002).

11. Management and Reporting of AEs/Adverse Reactions

11.1. Primary Data Collection Study

The study personnel will collect via data collection forms the below list of protocol-defined AEs, including all associated fatal outcomes, occurring in temporal association with lebrikizumab and the comparator product, as applicable, that are under evaluation in this protocol. The protocol-defined AEs will be summarized in the final study report and include

- SAB
- Stillbirth
- Elective termination
- Preterm delivery
- Congenital malformations (major structural birth defects or pattern of minor structural birth defects)
- SGA
- Postnatal growth up to one year of life (in live born infants)
- Serious infections up to one year of life (in live born infants), and
- Neonatal death.

All other AEs will not be actively collected because they are outside the scope of the research objectives for this study.

Non–protocol-defined adverse drug reactions may be reported in the course of participant interviews. Study personnel will report any event with specific attribution by the provider or the participant to lebrikizumab (that is, suspected adverse reactions) by the participant or a health care provider to Lilly. Study personnel are requested to report any suspected adverse reactions with other Lilly or non-Lilly products to the appropriate party as they would in normal practice.

Study personnel are not obligated to actively collect AEs or SAEs in patients once they have discontinued from the study. However, if the study personnel learn of any SAE, including death, at any time after the patient has discontinued from the study and the event is considered reasonably possibly related to the Lilly product under evaluation by the provider or the participant, the study personnel must promptly notify Lilly.

Further details regarding the event reporting and SAE reconciliation will be described in the safety management plan.

11.1.1. Serious Adverse Events

The study personnel will report to Lilly or its designee any protocol-defined SAE arising in temporal association with the Lilly product under evaluation within 24 hours of awareness of the event via a sponsor-approved method. Reports will be sent using the MedWatch form. A

protocol-defined SAE is any protocol-defined AE from this study that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect, or
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

The protocol defined AEs of this study that would meet this criteria for seriousness include

- Pregnancy ending in SAB
- Pregnancy ending in stillbirth or neonatal death
- Pregnancy ending in elective termination
- Major structural birth defect in the fetus or infant
- Serious infection (infection requiring hospitalization), and
- Death of infant.

Any other protocol-defined AE resulting in hospitalization of the mother or maternal death would also be reported as an SAE.

11.1.2. Nonserious AEs

The study personnel will record any nonserious, protocol-defined AEs arising in temporal association with the Lilly product under evaluation via data collection forms. These events will be reported as a listing in the annual report. The protocol-defined AEs that are considered nonserious are

- SGA
- Preterm birth, and
- Postnatal growth of live born children up to 1 year of age.

11.2. Product Complaints

Lilly collects product complaints on marketed Lilly products such as drugs, drug/device combinations, medical devices, software as medical device (for example, mobile medical applications), and comparator products used in postmarketing medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

For Lilly products under evaluation, Lilly products not under evaluation but discovered in the course of the study, or both, study personnel are instructed to report product complaints as they would for products in the marketplace.

For non-Lilly products, such as comparator drugs or medical devices, or concomitant drugs or medical devices, study personnel are instructed to report product complaints as they would for products in the marketplace.

12. Plans for Disseminating and Communicating Study Results

A final report describing the study outcomes will be prepared by the registry and provided to Lilly. Lilly will communicate the results to the FDA and any other relevant regulatory authorities. The study, including the final report, will also be registered in the HMA-EMA Catalogue of RWD studies. Scientific disclosures (that is, presentations for scientific and professional meetings or peer reviewed publications) will also be produced during the course of the study for the purposes of raising awareness of the study and communicating results.

13. Administrative Considerations

13.1. Responsibilities

13.1.1. Scientific Advisory Board

An external Scientific Advisory Board will be maintained by the registry and will review the registry summary data on an annual basis.

The Scientific Advisory Board is comprised of: 1) a Maternal-Fetal Medicine specialist with training in teratology, 2) a geneticist/dysmorphologist with expertise in teratology and birth defects, 3) an epidemiologist with expertise in teratology and birth defects, and 4) a dermatologist. If lebrikizumab is marketed for other indications, specialists treating those conditions will be added to the board. The board is chaired by a designated member, and each member has 1 vote. A dedicated charter describes roles and responsibilities of the board members, and members complete conflict of interest disclosures on an annual basis. The charter will detail a plan developed by the Scientific Advisory Board outlining what constitutes a signal for a birth defect, how it is reviewed, and what action might be taken should such a signal be seen.

Members of the board provide advice to the registry investigators on interpretation of the data and provide advice on strategies for the dissemination of information regarding the registry.

The annual and final reports will be finalized after Scientific Advisory Board meetings, in which the aggregate data will be discussed and reviewed.

13.1.2. Lilly

Lilly provides financial support for the registry and will support referrals to the registry. Lilly will work with the registry investigators to ensure that objectives are being met and that the registry staff are assisting Lilly in meeting its regulatory reporting responsibilities.

13.1.3. Study Investigators and the OTIS Research Center

The OTIS Research Coordinating Center is responsible for the following: collection, management, and follow-up of the reports of pregnancy exposures to the registry; conducting the analysis of the data; updating of the Registry Annual and Final Reports; interpretation of the findings; and preparation of publications resulting from the Registry. In addition, the Research Coordinating Center schedules, plans, and conducts Scientific Advisory Board meetings and forwards reports of major structural birth defects, SABs/miscarriages, stillbirths, elective terminations/abortions, or neonatal deaths occurring in lebrikizumab-exposed pregnancies enrolled in the registry to Lilly within 24 hours of becoming aware of the event. The Research Coordinating Center is responsible for increasing awareness of the registry through direct mailings, contacting groups and organizations who might be sources of referrals, and promoting the project at professional meetings, social media, as well as presenting results in abstracts and publications in scientific journals. The Research Coordinating Center is also responsible for communicating final results of the cohort study to the study participants.

The study investigators from the Research Coordinating Center are responsible for the conduct of the registry. Project management activities include, managing the Research Coordinating Center staff and activities, analysis of data that is collected as part of the registry, development of reports and other publications, maintaining current IRB approval, and communicating with Lilly and the Scientific Advisory Board who will meet at least on an annual basis.

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Appendix 1. List of Systemic Treatments Considered for Comparator Cohort

Systemic Medications	Days Equivalent to 5 Times the Half-Life[a,b]
Azathioprine	1
Calcineurin inhibitors (oral), including	
Cyclosporine	6
Tacrolimus	8
Voclosporin	8
Corticosteroids, systemic (oral or injected)	Medication dependent
Janus kinase (JAK) inhibitors (oral), including	
Abrocitinib	1
Baricitinib	4
Tofacitinib	2
Updacitinib	3
Methotrexate	3
Mycophenolate mofetil	4
Nemolizumab	95
Omalizumab	130
Ustekinumab	228

[a] Information on half-lives from Micromedex (https://www.micromedexsolutions.com).

[b] When elimination half-life provided was a range, the maximum time to clearance is used.

Note: Other medications and biosimilars in the comparator cohort class may be added, as applicable, during the course of the study.

Appendix 2. Dysmorphology Exam Checklist

Child's Name:_____ **Preg ID:**_____
Mother's Name:_____ **Study:**_____
Child's DOB:_____ **Exam Date:**_____

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Version 3

Calvarium	+	Eval	No Exam
Bifrontal Diameter Narrow			
Frontal Bossing			
Metopic Ridge			
Metopic Suture Open			
Third Fontanel			
Large Anterior Fontanel			
Occiput Prominent			
Occiput Flat			
Hair Whorl Double			
Hair Whorl Triple			
Hair Whorl Absent			
Hair Whorl Midline			
Hair Pattern Unruly			
Frontal Upsweep			
High Frontal Hairline			
Widow's Peak			
Hypopigmented Hair Patches			
Absent / Sparse / Patchy Hair, Specify:			
Scalp Defect			
Plagiocephaly			
Sutural Synostosis, Specify:			
Other, Specify:			
Face	**+**	**Eval**	**No Exam**
Supraorbital Ridges			
Prominent			
Hypoplastic			
Eyebrows			
Synophrys			
Medial Flare			
Other, Specify:			
Maxillary Hypoplasia			
Nasal Bridge			
Flat			
Prominent / Broad			
Nose:			
Short Nose			
Bulbous tip			
Broad Alar Base			
Nostrils:			
Anteverted			
Hypoplastic			
Thickened			
Short Columella			
Other, Specify:			
Philtrum smooth			
Vermillion Thin			
Cupid's Bow Missing			
Facial Asymmetry			
Other, Specify:			

Eyes	+	Eval	No Exam
Epicanthal Folds			
Left			
Right			
Ptosis			
Left			
Right			
Eyelashes			
Absent			
Other, Specify:			
Strabismus			
Other, Specify:			
Mouth	**+**	**Eval**	**No Exam**
CLEFT LIP			
Cleft Alveolar Ridge			
CLEFT PALATE			
Micrognathia			
Prognathia			
Macroglossia			
Microglossia			
Other, Specify:			
Ears	**+**	**Eval**	**No Exam**
MICROTIA/ANOTIA			
Preauricular Pit			
Left			
Right			
Prominent Median Bar			
Preauricular Tag			
Left			
Right			
Other, Specify:			
Neck	**+**	**Eval**	**No Exam**
Webbed			
Short			
Broad			
Low Post Hair Line			
Branchial Sinus			
Torticollis			
Other, Specify:			
Chest and Abdomen	**+**	**Eval**	**No Exam**
Supernumerary Nipples			
Left			
Right			
Poland Sequence			
Pectus Excavatum			
Pectus Carinatum			
Diastasis Recti			
Umbilical Hernia			
Other, Specify:			
Back	**+**	**Eval**	**No Exam**
Lumbar Dimple or other cutaneous marker, Specify:			
Sacral dimple or other cutaneous marker, Specify:			
SCOLIOSIS			
LORDOSIS			
KYPHOSIS			
Other, Specify:			

Preg ID:_____

Telemedicine
Dysmorph Exam Form

Version 3

Arms	+	Eval	No Exam
Incomplete Pronation / Supination			
Other, Specify:			
Hands	**+**	**Eval**	**No Exam**
Single Transverse Palmar Crease			
Left			
Right			
Thenar Crease Absent			
Left			
Right			
Abnormal Palmar Creases Other, Specify:			
Clinodactyly 5th Finger			
Left			
Right			
Broad thumb			
Left			
Right			
Thumb Hypoplasia			
Left			
Right			
Fingers Tapered			
Fingers Overlapping			
Finger Tip Pads Prominent			
Interphalangeal Creases Absent			
Left PIP: 2_3_4_5_			
Left DIP: 2_3_4_5_			
Right PIP: 2_3_4_5_			
Right DIP: 2_3_4_5_			
Right thumb IP			
Left thumb IP			
IP Creases Extra			
Fingers			
Left			
Right			
POLYDACTYLY, Specify (type and side)			
Preaxial			
Postaxial			
Insertional			
OLIGODACTYLY, Specify:			
Syndactyly, Specify (side and fingers involved)			
Fingernails			
Absent			
Hypoplastic			
Hyperconvex			
Other, Specify:			
Legs	**+**	**Eval**	**No Exam**
Leg length discrepancy			
Genu Valgum			
Genu Varus			
Patella Absent			
Other, Specify:			

Feet	+	Eval	No Exam
Club foot			
Left			
Right			
Metatarsus adductus			
Left			
Right			
Other Foot Deformity, Specify:			
Heels Prominent			
Left			
Right			
Space increase 1-2 toes			
Left			
Right			
Broad 1st Toes			
Left			
Right			
Toes Overlapping – Other, Specify (type and side):			
POLYDACTYLY, Specify (type and side)*:*			
Preaxial			
Postaxial			
Insertional			
OLIGODACTYLY, Specify:			
Syndactyly, Specify (side and toes involved)			
Toenails			
Absent			
Hypoplastic			
Hyperconvex			
Other, Specify:			
Skin	**+**	**Eval**	**No Exam**
Capillary Hemangioma (count only if ≥ 1.5 cm, or multiple of any size) || Size:_____ **Location:*			
Vascular Malformation			
Glabella Size:			
Neck Size:			
Eye Lids Size:			
Crown Size:			
Other **Location:* Size:			
Port-wine Stain			
Café-Au-Lait (count only if ≥ 1.5 cm or ≥ 6 CAF spots)			
Nevus Sebaceous			
Hirsutism			
Hypertrichosis			
Hypopigmented Skin Changes, Specify:			
Pigmented Nevus			
Other, Specify:			
Joints	**+**	**Eval**	**No Exam**
Contracture, Specify:			
Laxity			
Dislocation			
Pterygia			
Other, Specify:			
Neurologic	**+**	**Eval**	**No Exam**
Hypotonia			
Hypertonia			
Other, Specify:			

Preg ID:_____

Telemedicine
Dysmorph Exam Form

Version 3

Child's Age:_____

	Measurement:	Percentile:
OFC		

Macrocephaly >97th centile

Microcephaly <3rd centile

Total Number of Minor Malformations: _____

List Minor Malformations (indicate NC by those not counted):

Major Malformations:

Additional Comments:

Physician Name:_____

Physician Signature:_____

Appendix 3. List of Teratogens

Known Human Teratogens[a]		Possible Human Teratogens[b]		Suspected Human Teratogens[c]	
Exposure[d]	**Notes[e]**	**Exposure**	**Notes[e]**	**Exposure**	**Notes[e]**
Androgens	Includes: Danazol	I-131 radioactive iodine	Exposure after 10 weeks postconception	Azathioprine	
Angiotensin-Converting Enzyme (ACE) Inhibitors	Exposure after 11 weeks from DOC	Aflibercept		Leflunomide	
Angiotensin II Receptor Blockers (ARBs)	Exposure after 11 weeks from DOC	Endothelin receptor antagonists for treatment of pulmonary hypertension or nephropathy	Includes: macitentan ambrisentan bosentan sparsentan	Paroxetine	
Alcohol, Heavy	>14 drinks per week for ≥4 weeks.	Riociguat		Teriflunomide	
Aminopterin		Pomalidomide			
Antiseizure/ Anticonvulsant Medications		Azacytidine			
Antineoplastics, All					
Cocaine					
Cyclophosphamide					
Cytomegalovirus (CMV)					
Diabetes, Type I and Type II					
Diethylstilbesterol					
Fever, High	102 degrees or higher for 24 hours or longer				
Fluconazole	≥7 days total (consecutive or nonconsecutive), 400-800 mg/day dose, or both				
Lenalidomide (Analog of Thalidomide)					
Lithium					
Methimazole					

Known Human Teratogens[a]		Possible Human Teratogens[b]		Suspected Human Teratogens[c]	
Exposure[d]	Notes[e]	Exposure	Notes[e]	Exposure	Notes[e]
Methotrexate					
Misoprostol					
Mycophenolate Mofetil					
Penicillamine					
Propylthiouracil (PTU)					
Radiation, High Dose	≥5 rads to the uterus				
Retinoids, Systemic	Includes: acitretin within 2 years prior to DOC, etretinate exposure ever, isotretinoin				
Rubella					
Tetracyclines (Tetracycline, Doxycycline, Minocycline, Tigecycline)	Exposure after 12 weeks from DOC				
Thalidomide					
Toxoplasmosis					
Varicella	Primary infection (primary case of chicken pox)				
Vitamin A	High dose, >30,000 IU				
Warfarin (Coumadin, Jantoven) Derivatives	Includes coumadin derivatives: acenocoumarol dicumarol phenprocoumon fenprocoumon				
Zika, Confirmed	Positive test result				

Abbreviation: DOC = date of conception.

[a] List of known human teratogens that have been demonstrated in multiple studies to cause birth defects in humans.

[b] List of possible human teratogens that have no human data but included based on the drug class or mechanism of action.

[c] List of suspected human teratogens for which there are either animal data that show concern, but human data do not confirm teratogenicity, or there are conflicting human data.

[d] Other human teratogens may be added, during the course of the study, as applicable.

[e] The default timeframe for exposure is from DOC for any medications where the information is not listed in the notes.