STUDY PROTOCOL

Study Information

Title	Apremilast Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project
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PROTOCOL SIGNATURE PAGE

Apremilast pregnancy exposure registry : OTIS Autoimmune diseases in pregnancy project

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
NCHS	National Center for Health Statistics
OTIS	Organization of Teratology Information Specialists
PsO	Psoriasis
PsA	Psoriatic Arthritis
SAE	Serious Adverse Event
US	United States

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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3. ABSTRACT

The Apremilast Pregnancy Exposure Registry (Registry) is a United States (U.S.) based registry designed to monitor planned or unplanned pregnancies exposed to apremilast when used to treat an approved indication in accordance with the current approved prescribing information, who reside in the U.S. or Canada. As of June 1st 2014 apremilast is currently approved in the U.S for use in psoriatic arthritis with potentially further approvals in psoriasis and ankylosing spondylitis. Similar approved indications are anticipated in Canada. The Registry fulfills a post-marketing commitment to the Food and Drug Agency (FDA).

The goal of the Registry is to conduct an observational, controlled prospective cohort study that will involve follow-up of live born infants to one year of age. The study population includes pregnant women who reside in the U.S. or Canada who have or have not used apremilast for any length of time in pregnancy for an approved indication. The cohort study target sample size is 100 pregnant women in each of three groups:

- 100 women who have been exposed to apremilast in pregnancy for an approved indication.
- 100 women with an approved disease who have not been exposed to apremilast at any time in pregnancy (primary comparison group).
- 100 healthy women who have no diagnosis of an approved indication or other chronic illness and have not taken apremilast in pregnancy.

. The primary objective of the Registry is to evaluate any potential increase in the risk of major birth defects, specifically a pattern of anomalies, in apremilast exposed pregnancies compared to the primary comparison group of disease-matched unexposed pregnancies. Secondary objectives are to evaluate the potential effect of exposure relative to the secondary comparison group of healthy pregnant women, and the effect of exposure on other adverse pregnancy outcomes including spontaneous abortion or stillbirth, preterm delivery, reduced infant birth size, a pattern of minor malformations, postnatal growth of live born children to one year of age, and incidence of serious or opportunistic infections or malignancies in live born children up to one year of age.

The Pregnancy Exposure Registry is sponsored by Celgene Corporation and is conducted by the Organization of Teratology Information Specialists (OTIS) Research Group and is administered by investigators at the coordinating site located at the University of California, San Diego. The study is planned for seven years, with an annual interim report reviewed by the Scientific Advisory Board. The final report with statistical analysis according to the statistical analysis plan will be prepared at the end of the study.

4. AMENDMENTS AND UPDATES

All amendments and updates to this protocol will be documented in the table below.

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason

5. MILESTONES

Milestone[1]	Planned date
Contract Signed	30 July 2014
IRB Approval	30 August 2014
Start of data collection	30 August 2014
Study progress report 1	30 August 2015
End of data collection	30 February 2021
Final study report	30 July 2021

6. RATIONALE AND BACKGROUND

Many immune-mediated diseases affect women of childbearing potential and the medications used to treat these diseases may affect conception, pregnancy, and fetal development (Skomsvoll, 2001). Although improvement of some immune-mediated disease activity spontaneously occurs in a proportion of pregnancies, many women still require treatment during pregnancy. In addition, as approximately half of pregnancies in the U.S. are not planned, there is potential for inadvertent early pregnancy exposure to medications in an unplanned pregnancy.

Apremilast (CC-10004) is a new drug that is taken orally (by mouth; PO). Apremilast works by inhibiting the enzyme phosphodiesterase 4 (PDE4), which is found inside cells of the immune system. By inhibiting PDE4, apremilast reduces inflammation in the body caused by diseases such as psoriasis (PsO) and psoriatic arthritis (PsA).

Apremilast has been under clinical development for the treatment of several immune-mediated inflammatory disorders that involve elevated cytokine levels, such as PsO, PsA, Behçet's disease, ankylosing spondylitis, and inflammatory bowel disease. Apremilast is currently approved within the United States for use in patients with active PsA. Potential additional regulatory approvals for indications including, but not limited to, PsO and ankylosing spondylitis are anticipated. Similar approvals are anticipated in Canada. The approved indications may therefore be expanded during the course of this study. Prior to initiation of recruitment OTIS staff and recruitment centers will be informed of the approved indications for apremilast and made aware should additional indications be approved.

6.1. Preclinical Studies with Apremilast

Apremilast is not genotoxic or carcinogenic. Reproductive and developmental effects of apremilast included prolongation of estrous cycles in mice, prenatal embryo-fetal loss in mice and monkeys, and delayed fetal development (reduced ossification and fetal weight) in mice. Apremilast was not teratogenic in animals; no treatment-related malformations were observed up to 750 and 1000 mg/kg/day in mice and monkeys, respectively. The No Observed Adverse Event Level (NOAEL) for male fertility was 50 mg/kg/day (2.9-fold increase over clinical AUC), and the no-observed-effect level (NOEL) for female fertility was 10 mg/kg/day (1.0-fold increase over clinical AUC). In the embryo-fetal development studies, the maternal and developmental NOEL/NOAELs in mice and monkeys were 10 and 20 mg/kg/day (1.3- and 1.4-fold increase over clinical AUC), respectively. In a pre- and postnatal study in mice, maternal clinical signs associated with delivering pups, and increased peri- and postnatal pup mortality and reduced pup body weights through lactation day 7, were observed at 80 and 300 mg/kg/day; the NOEL for maternal toxicity and F1 generation was 10 mg/kg/day (1.3-fold increase over clinical AUC) (Celgene 2013).

6.2. Clinical Studies with Apremilast

Apremilast is labeled as a Pregnancy Category C therapy. At the time of approval there were no adequate and well-controlled studies of apremilast in pregnant women. The label specifies that apremilast should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether apremilast or its metabolites have an effect on fertility.

7. RESEARCH QUESTION AND OBJECTIVES

The purpose of the Apremilast Pregnancy Exposure Registry is to monitor planned and unplanned pregnancies exposed to apremilast and to evaluate the possible teratogenic effect of this medication relative to specified pregnancy outcomes, and to evaluate potential effects of prenatal apremilast exposure on infant health status through one year of age. The lack of human fetal safety data for apremilast makes such a monitoring system an important component of epidemiologic research on the safety of this drug.

The Registry supports a post-marketing commitment to the U.S. Food and Drug Agency (FDA).

7.1. Objectives

The **primary** objective of the Registry is to evaluate whether there is any increased risk of major birth defects, specifically a pattern of anomalies in apremilast-exposed pregnancies compared to the **primary** comparison group of disease-matched unexposed pregnancies. The **secondary** objectives of the Registry are to determine if there is an increase in the risk of spontaneous abortion, stillbirth or preterm delivery in apremilast-exposed pregnancies compared to disease-matched unexposed pregnancies, and among live born infants, to determine if there is an increase in the risk of a specific pattern of minor anomalies, reduced birth size, postnatal growth deficiency up to one year of age, and serious or opportunistic infections or malignancies up through one year of age in apremilast-exposed pregnancies

compared to the **primary** comparison group of disease-matched unexposed pregnancies. Additional **secondary** objectives of the Registry are to compare the risk for each of the specified outcomes in apremilast-exposed pregnancies to a **secondary** comparison group of healthy women who have no diagnosis of an approved indication or other chronic illness, have not had exposure to a known human teratogen, and have not taken apremilast in pregnancy. A **tertiary** objective of the Registry is to compare the rate of major birth defects in the apremilast-exposed pregnancies to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance program (Centers for Disease Control and Prevention, 1998).

8. RESEARCH METHODS

8.1. Study design

This is a prospective, observational, exposure cohort study of pregnancy outcome in women who are exposed to apremilast during pregnancy for an approved indication compared to pregnancy outcome in a diseased comparison group women who have not used apremilast during pregnancy (disease-matched unexposed comparison group), and pregnancy outcome in healthy women who have no diagnosis of an approved indication or other chronic illness, have not had exposure to a known human teratogen, and have not taken apremilast in pregnancy (non-disease comparison group).

Exposure to apremilast is considered as the oral administration of any dose for any duration of time. Apremilast is currently approved within the United States for use in patients with active PsA. However, there remains the potential for additional approvals to be added during the course of this study. Prior to initiation of recruitment OTIS staff and recruitment sites will be informed of the approved indications for apremilast and made aware should additional indications be approved.

8.2. Setting

The Registry cohort study will be conducted by the Organization of Teratology Information Specialists (OTIS) which is a network of university and health department based telephone information centers serving pregnant women and healthcare providers throughout North America (Leen-Mitchell, 2000). These services receive spontaneous telephone inquiries from women and health care providers about the safety or risk associated with environmental exposures in pregnancy, including medications. Trained Teratogen Information Specialists at each site provide appropriate risk assessment and referral for all patient and health care provider callers free of charge. These services also provide a basis for collaborative research such as this Registry. Thus, individual Teratogen Information Services located throughout the U.S. and Canada will serve as a source of referrals not only for apremilast-exposed pregnancies but also for similarly-ascertained disease-matched comparison pregnant women who have not used apremilast in pregnancy and similarly-ascertained non-disease pregnant

women who have no diagnosis of an approved indication or other chronic illness, have not had exposure to a known human teratogen, and have not taken apremilast in pregnancy.

As OTIS member services receive over 70,000 teratogen information telephone inquiries per year, 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 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 establishing cohort inclusion criteria that require enrollment prior to 19 completed weeks' gestation, and 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 ultrasound, and allow for better estimation of risk of spontaneous abortion.

The study population includes pregnant women who reside in the U.S. or Canada with apremilast-exposure for any approved indication, and two comparison groups without apremilast exposure during pregnancy (one disease-matched unexposed comparison group, and one non-diseased unexposed comparison group). Based on use of multiple methods for identification and recruitment of exposed women, and the previous recruitment experience of the existing OTIS studies (Jones, 2002), we have projected that approximately 20 pregnant women with exposure to the apremilast could be enrolled in the Registry each year, although the true number of exposed pregnancies potentially available for enrollment in the Registry cannot be known at this time.

8.3. Variables

Key exposure, outcome and potential confounding variables are defined below. Additional details regarding definitions are provided in the Statistical Analysis Plan to be developed separately.

Exposure Variable:

- Maternal report of exposure to apremilast of at least one oral dose any time from first day of last menstrual period (LMP) to end of pregnancy (defined as full term delivery, abortion, miscarriage or stillbirth)
- Dose of apremilast in mg per day
- Duration (weeks) of apremilast use in pregnancy (LMP to conception only, 0-2, 2.1-4, 4.1-6, >6 weeks of gestation)
- Indication for use of apremilast

Outcome Variables:

- <u>Primary</u>

- A major structural defect is defined as a defect which occurs in less than 4 percent of the population and which has either cosmetic or functional significance to the child (e.g., a cleft lip) and is identified up to 1 year of age and coded using the U.S. Centers for Disease Control Metropolitan Atlanta coding system.

- Secondary
  - A minor structural defect is defined as a defect which occurs infrequently in the population but which has neither cosmetic nor functional significance to the child and is identified using a study-related checklist incorporated into the study dysmorphology examination of live born infants.
  - Spontaneous abortion is defined as non-deliberate embryonic or fetal death that occurs prior to 20 weeks' gestation post-LMP.
  - Stillbirth is defined as a non-deliberate fetal death that occurs at or after 20 weeks' gestation but prior to delivery.
  - Premature delivery is defined as live birth prior to 37 weeks' gestation as counted from LMP
  - Small for gestational age is defined as birth size (weight, length or head circumference) less than or equal to the 10th percentile for sex and gestational age using National Center for Health Statistics (NCHS) pediatric growth curves for full term infants. Prenatal growth curves specific to preterm infants will be used for premature infants.
  - Postnatal growth deficiency is defined as postnatal size (weight, length or head circumference) less than or equal to the 10th percentile for sex and age using NCHS pediatric growth curves, and adjusted postnatal age for premature infants.
  - Lost-to-follow-up is defined as an enrolled subject who fails to complete the outcome interview despite a standard number of telephone attempts and attempts to contact by mail as per study procedure manual within 1 year of the mother's estimated due date. Voluntary subject withdrawals will be considered separately.
  - Serious or opportunistic infections are defined as those listed in the appendix or any others that are reported and identified in infants up to 1 year of age, or infections that require hospitalization for any length of time identified up to 1 year of age.
  - Malignancies are defined as any malignancy reported in an infant up to 1 year of age.

Potential Confounders Include But Are Not Limited To:

- Maternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34)
- Maternal race (Caucasian/White, Black, Asian, Pacific Islander, Native American, Other)
- Maternal ethnicity (Hispanic, Non-Hispanic)
- Maternal Educational Category (years of completed education <12, 12-15, >15)
- Hollingshead Socioeconomic Category based on maternal and paternal occupation and education (1-5)
- Maternal height (cm)
- Maternal pre-pregnancy body weight (kg)
- Maternal pre-Pregnancy BMI (<18.5, 18.5-24.9, 25-29.9, >=30)
- Number of times ever pregnant (1, 2-3, 4-5, >=6)
- Number of previous live birth or stillbirth deliveries (0, 1-2, 3-4, >=5)

- Number of previous pregnancies ending in spontaneous abortion (0, 1, 2, >=3)
- Number of previous pregnancies ending in elective termination (0, 1, 2, >=3)
- Gestational age (weeks) of pregnancy at time of enrollment, continuous and categorical (<13, 13-19.9, >=20): gestational age is calculated from the first date of LMP.
- Referral source (Sponsor, OTIS service, HCP, Internet, Other)
- Geographic area of residence (US, Canada)
- Disease Severity Scores (exposed and disease-matched cohorts only)
- Prenatal, Multivitamin or Folic Acid supplement use by timing (began prior to conception, post-conception only, not taken at all)
- Alcohol use in pregnancy (yes/no)
- Tobacco use in pregnancy (yes/no)
- Prenatal diagnostic tests performed prior to enrollment (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis)
- Prenatal diagnostic tests performed anytime in pregnancy (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis)
- Maternal pregnancy exposure to another known human teratogen (e.g. methotrexate)
- Years since diagnosis of indicated approved disease

8.4. Data sources

8.4.1. Registry Procedures for Cohort Study

Although the Registry will collect and follow up on reports of all types (i.e., retrospective, paternal, exposure after first trimester only, off-label indication, etc., see Section 9.10) involving pregnancy exposure to apremilast, the core of the Registry will be a prospective cohort study designed to ascertain and follow-up on first-trimester pregnancy exposures to apremilast and to compare these outcomes to two internally-generated comparison groups and one external comparison group (MACDP). Participating centers will be Teratology Information Services (TIS) or individuals who are members of the Organization of Teratology Information Specialists (OTIS) in North America and who agree to the study protocol as established by the OTIS Research Committee and described herein. In addition to an exposed group, two comparison groups will be enrolled using the same OTIS-based and other sources of recruitment.

- Comparison Group I consisting of diseased-matched pregnant women who have not been exposed to apremilast at any time in the current pregnancy. This will be the primary comparison group.
- Comparison Group II consisting of pregnant women who contact an OTIS member service or who contact the study directly and who do not have an approved disease or other chronic illness, have not been exposed to a known human teratogen, and have not taken apremilast in pregnancy. This will be a secondary comparison group.

- Based on experience, it is estimated that Comparison Group II will likely be similar to the exposed and primary comparison group on key demographics such as maternal age, socioeconomic status and race/ethnic distribution; however, should differences occur, they will be addressed in the analysis phase.
- For the frequency of major structural defects in the apremilast-exposed group, an external comparison will also be made to the Metropolitan Atlanta Congenital Defects Program (MACDP), which is a population-based birth defects surveillance program in the U.S. with careful follow-up and classification of major structural defects identified up to one year of age. This particular program is considered appropriate for external comparison given the fact that it is population based and includes a relatively high level of validation of reported defects identified in children up to one year of age. The overall rate of major birth defects identified in the MACDP (approximately 3% in 2005) is comparable to the overall rates (2-3%) identified in larger samples of Teratogen Information Service cohort studies that involve a careful review of medical records and physician examinations.

8.4.2. Apremilast-Exposed Subject Selection for Cohort Study

8.4.2.1. Apremilast-Exposed Group - Inclusion Criteria

Subjects enrolled in the apremilast-exposed group should meet the following criteria

- Pregnant women who have had an oral exposure to apremilast for the treatment of an approved indication, for any number of days, at any dose, and at anytime from the 1st day of the last menstrual period up to and including the 12th week after the first day of the last menstrual period (LMP). If the date of LMP is unclear, or if a first-trimester ultrasound has been done and the estimated date of conception is more than one week discrepant from the menstrual period calculation, the first-trimester ultrasound-derived date will be used to calculate a date for LMP and conception
- Enroll no later than 19 completed weeks from LMP and who have not had prenatal diagnosis in the current pregnancy of any major structural defect
- Agree to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.

8.4.2.2. Apremilast-Exposed Group - Exclusion Criteria

- Women with exposures commencing after the 12th week post-LMP
- Women who are greater than 19 completed weeks' gestation prior to enrollment
- Women who have first contact with the project after prenatal diagnosis of any major structural defect

- Women who have enrolled in the cohort study with a previous pregnancy
- Women who have used apremilast for an indication other that is not a currently approved indication
- Other retrospective reports (see Section 9.10).

8.4.3. Internal Comparison Group Subject Selection for Cohort Study

8.4.3.1. Comparison Group I – Inclusion Criteria

Subjects enrolled in the non-exposed, disease-matched comparison group I should meet the following criteria

- Currently pregnant women approximately frequency matched to the exposed group by disease indication, validated by medical records, who have not been exposed to apremilast any time in the current pregnancy but who may or may not have been exposed to apremilast previous to the current pregnancy, and may or may not have taken another medication for their disease in the current pregnancy
- Enroll no later than 19 completed weeks' gestation and who have not had prenatal diagnosis in the current pregnancy of any major structural defect
- Agree to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.

8.4.3.2. Comparison Group I – Exclusion Criteria

- Women who are greater than 19 completed weeks gestation prior to enrollment,
- Women who have first contact with the project after prenatal diagnosis of any major structural defect
- Women who have enrolled in the cohort study with a previous pregnancy
- Women who enroll retrospectively.

8.4.3.3. Comparison Group II – Inclusion Criteria

Subjects enrolled in the non-exposed, non-disease comparison Group II should meet the following criteria

- Currently pregnant women who have not had exposure to a known human teratogen as confirmed by the OTIS Research Center,

- Do not currently have any approved indication or other chronic disease,
- Enroll no later than 19 completed weeks' gestation,
- Have not had prenatal diagnosis in the current pregnancy of any major structural defect prior to enrollment, and
- Agree to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.

8.4.3.4. Comparison Group II – Exclusion Criteria

- Currently pregnant women who incur an exposure to a known teratogen in the first trimester after the time of enrollment will be disqualified as subjects for purposes of the analysis
- Women who have a diagnosis of an approved indication or any other serious chronic disease that is thought to adversely impact pregnancy,
- Women who are greater than 19 completed weeks' gestation prior to enrollment
- Women who have first contact with the project after prenatal diagnosis of any major structural defect
- Women who have enrolled in the cohort study with a previous pregnancy
- Women who enroll retrospectively.

8.4.4. Recruitment for Cohort Study

All exposed subjects and comparison subjects will be recruited through spontaneous callers to participating OTIS member services in locations throughout North America and through active recruitment strategies, e.g., direct mailings to rheumatologists, dermatologists and other relevant specialists, obstetric health care providers, pharmacists, web site, and professional meetings. Each OTIS service will provide exposure counseling 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 explain the study protocol to potentially eligible participants, and then will request permission to refer to the Research Center at the University of California, San Diego. Potential subjects who agree to be referred will contact the Research Center or be contacted if they prefer. OTIS member services will also refer callers to the Research Center whose exposure to apremilast does not appear to qualify for the cohort study (e.g., first contact after 19 completed weeks' gestation) or retrospective reports, as these will be handled as Registry Exposure Case Reports (See Section 9.10). Health care providers can also contact the Registry and refer patients; however, in all cases the mother is the individual who provides informed consent for participation and completes the interview-based data collection.

8.4.5. Pregnancy Follow-up for Cohort Study

The OTIS Research Center is responsible for verifying the subject selection criteria, enrolling each subject and securing informed consent, oral and written, providing all pregnancy and post-partum follow-up interviews and medical record review, scheduling dysmorphological examinations, recording and storage of all data, and subsequent data analysis.

8.4.5.1. Intake Interview for Cohort Study

Following verbal explanation of the informed consent and the HIPAA Authorization Addendum, a structured maternal intake telephone interview will be conducted by a trained Research Associate at the OTIS Research Center. This interview will include questions on the following: pregnancy history; current health history; pre-pregnancy weight and height; socioeconomic and demographic information including maternal and paternal occupation, education and ethnicity; income category, current medication use, both prescriptive and over the counter; other environmental or occupational exposures, alcohol, tobacco, caffeine and illicit drug use; current pregnancy complications including illnesses; and history of onset and other characteristics of the autoimmune disease the participant is enrolled for, if applicable. Women who are enrolled with an indicated disease will be asked to respond to a severity assessment questionnaire that is specific to the approved indication to provide a means of assessing potential confounding or effect modification by disease severity in the final analysis.

8.4.5.2. Interim Interviews for Cohort Study

Following the initial intake interview, participants will be sent a pregnancy diary on which they will be asked to record any additional exposures (medications, vaccinations, vitamins, etc.) or events as the pregnancy progresses. Along with the pregnancy diary, each woman will be sent a copy of the written informed consent document. Women who have enrolled in the study prior to 16 weeks post-LMP will be interviewed by telephone at 20-22 weeks post-LMP, 32-34 weeks post-LMP and within two to six weeks after the expected due date. Women who have enrolled between 16 and 20 weeks post-LMP will be interviewed at 32-34 weeks post-LMP and within two to six weeks after the expected due date (See Table 1 Schedule of Follow-up). The purpose of these interviews will be to update records of pregnancy exposures and results of prenatal tests, to remind women to maintain the exposure diary, to update phone number and address information, and to determine if the pregnancy has ended prior to the expected due date.

8.4.5.3. Outcome Interview for Cohort Study

- 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 32-34 week interview, the

outcome interview will be conducted within two to six weeks after the expected due date.

- The outcome interview for live born infants will be 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.
- The outcome interview for spontaneous or elective abortions will also be structured and 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 interview. The outcome interview for stillborn infants will include all of the above plus information on sex, birth size and autopsy results if available.
- Major structural defects, spontaneous abortions, elective terminations, fetal or neonatal deaths occurring in the apremilast-exposed group will be reported to the Sponsor within 24 hours of the Research Center staff learning of the event. These reports will be made using the FDA's MedWatch form. The Sponsor will be responsible for directly reporting to the FDA for events involving their product according to regulatory guidelines.

8.4.5.4. Medical Records and General Pediatric Evaluation

- Upon completion of the outcome interview, each woman will be mailed a packet containing medical records release forms for the delivery hospital, obstetrician, pediatrician, and specialty physician if applicable. For women whose pregnancies have ended in spontaneous or elective abortion or stillbirth, records release forms will be mailed for prenatal diagnosis, pathology or autopsy reports if available. Each woman will be asked to sign the forms, as well as and HIPAA Authorization Addendum, and to return these consents 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 congenital anomalies.
- At one year of age, another medical records release form for the pediatrician or health care provider caring for the child is sent to the mother for signature, and the signed form with a standard physical evaluation form is sent to the health care provider to request updated information on growth, congenital defects, any

opportunistic infections (See Appendix 1), infections resulting in hospitalization and/or malignancies diagnosed up through one year of age.

8.4.5.5. Dysmorphological Evaluation

- Live born infants in the apremilast-exposed group and both comparison groups will be examined by one of a team of study-dedicated dysmorphologists, led by Co-Investigator, Kenneth Lyons Jones, M.D., from the University of California, San Diego, all licensed pediatricians with subspecialty fellowship training in dysmorphology/genetics. This team of physicians has been functioning as the specialist examiners for the current OTIS Autoimmune Diseases in Pregnancy Project and have completed examinations for well over 1,000 infants throughout North America as part of this protocol using the same standard procedures as are incorporated in this Registry. The physical examinations evaluate infants for both major and minor structural defects which 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, as is the protocol in the existing OTIS Autoimmune Diseases in Pregnancy Project. The Research Center will group and schedule these follow-up examinations to meet the study criteria of infant age, to maximize physician blinding as to exposure status, and to minimize travel time and expense.
- Infant examinations will be conducted using a standard checklist of approximately 130 minor malformations included in a standard physical evaluation form. In addition, with parental consent, digital photographs 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. Because subjects may have visible evidence of their disease, the use of a disease-matched comparison group allows for preservation of physician blinding.

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

	<20 weeks gestation	20-22 weeks gestation*	32-34 weeks gestation	0-6 weeks after delivery	0-12 months after delivery	1 year after delivery
Referral	√					
Enrollment and Consent	√					
Intake Interview	√					
Interim Interview I		√				
Interim Interview II			√			
Outcome Interview				√		
Dysmorphological Examination					√	
Pediatric Medical Record Review and Questionnaire at 1 Year						√

*If subject is enrolled and Intake Interview is conducted between 16 and 20 weeks' gestation, only one Interim Interview will be conducted during pregnancy at 32-34 weeks' gestation

8.4.6. Outcome Classification for the Primary Endpoint – Major Structural Defects

The method for classifying structural defects for purpose of analysis has been previously described by the study investigators and the OTIS Research Group (Chambers, 2001; Centers for Disease Control, 1998) and has been used in previous studies conducted by OTIS.

8.4.6.1. Criteria for Primary Endpoint for Cohort Study - Major Structural Defects

- *Definitions:*
  A major structural defect is defined as a defect which occurs in less than 4 percent of the population and which has either cosmetic or functional significance to the child (e.g., a cleft lip).
- Classification of major defects is performed according to the CDC coding list.
- *Time period for identification:* major structural defects identified up to one year of age by the mother, the health care provider/medical record, or identified in the

dysmorphological examination 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 that is ascertained by the examining dysmorphologist prior to one year of age will be included if it is confirmed as a heart defect by cardiac ultrasound. Similarly, a midline cutaneous marker at L2-L3 noted in the dysmorphological examination will be included as occult spinal dysraphism only if confirmed by appropriate imaging studies.

8.4.6.2. Exclusion Criteria for Primary Endpoint for Cohort Study - Major Structural Defects

- *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 spontaneous abortions or elective terminations:* Defects identified by prenatal ultrasound or examination of the products of conception following elective or spontaneous abortion will be not be included in the primary analysis due to potential bias involved in non-uniform use of prenatal diagnosis and pathology evaluation for all abortuses; however, these defects will be considered in a secondary analysis including all defects in the numerator over all pregnancies with known outcome in the denominator (excluding losses to follow-up).

8.4.7. Outcome Classification for Secondary Endpoints for Cohort Study

8.4.7.1. Definitions for Secondary Endpoints

- *Spontaneous abortion:* spontaneous abortion is defined as non-deliberate fetal death which occurs prior to 20 weeks post-LMP.
- *Elective abortion:* elective abortion is defined as deliberate termination of pregnancy at any time in gestation.
- *Stillbirth:* stillbirth is defined as non-deliberate fetal death anytime in gestation at or after 20 weeks post-LMP.
- *Premature delivery:* premature delivery is defined as live birth prior to 37 completed weeks gestation as counted from last menstrual period (or calculated from first-trimester ultrasound-derived due date if last menstrual period uncertain or more than one week discrepant). Elective caesarian deliveries or inductions prior to 37 completed weeks will be considered separately.
- *Small for gestational age:* small for gestational age is defined as birth size (weight, length or head circumference) less than or equal to the 10^{th} centile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm

infants (US National Center for Health Statistics, 2000; Nelhaus, 1968; Britton, 1993).

- *Postnatal growth deficiency:* postnatal growth deficiency is defined as postnatal size (weight, length or head circumference) less than or equal to the 10th centile for sex and age using NCHS pediatric growth curves, and adjusted postnatal age for premature infants if the postnatal measurement is obtained at less than one year of age.
- *Lost-to-follow-up:* Subjects will be considered lost-to-follow-up if they have completed the initial intake interview but subsequently fail to complete the outcome interview and medical records release despite repeated attempts after one year of the mother's estimated due date. Voluntary subject withdrawals will be considered separately.
- *Postnatal opportunistic infections, hospitalizations for serious infections, or malignancies:* Through the one-year postnatal follow-up period, pediatric records will be requested with specific requests for documentation of opportunistic infections (defined in Appendix I), hospitalizations for infections, or malignancies.
- *Minor malformations:* A minor structural defect is defined as a defect which occurs in less than 4 percent of the population but which has neither cosmetic nor functional significance to the child (e.g., complete 2,3 syndactyly of the toes). Minor malformations will be identified only through the study dysmorphology examination for live born infants using the study-specific checklist.

8.5. Study sample size

Recruitment goals are set at 20 subjects per year in each of the three groups as shown below in Table 2. It is not possible to predict the number of pregnancy exposures that will occur for a newly marketed medication, or that the recruitment rates will be equal in all years, and therefore, sample size is based on estimates that may require revision as the study progresses.

Table 2. Anticipated Recruitment Timetable and Sample Size

Year 1	Year 2	Year 3	Year 4	Year 5
Enroll 20 exposed 20 comparison I 20 comparison II	Enroll 20 exposed 20 comparison I 20 comparison II	Enroll 20 exposed 20 comparison I 20 comparison II	Enroll 20 exposed 20 comparison I 20 comparison II	Enroll 20 exposed 20 comparison I 20 comparison II

Based on previous experience with the OTIS studies,, we estimate that subjects will be an average of 7-10 weeks post-LMP at the time of enrollment. Given this mean gestational timing at enrollment, the anticipated spontaneous abortion and stillbirth rate is 10%, the estimated elective abortion rate is 10%, the estimated lost-to-follow-up rate is 5% (based on previous OTIS experience) resulting in approximately 75 live born infants in each group at the end of recruitment. Experience with current OTIS studies has demonstrated a yield of approximately 80% live born infants from the total proportion enrolled; therefore the estimated yield of 75% in this proposal is conservative. We estimate baseline rates of major structural defects, spontaneous abortion, premature delivery, and small for gestational age (SGA) and the standard deviation for mean birth weight of full-term infants based on previous OTIS studies and on general population data. With this sample size, at 80% power, alpha of 0.05, two-tailed tests of significance (except as noted for pattern of minor anomalies), and each comparison group independently compared to the exposed group, the following minimum effect sizes will be detectable:

Table 3. Sample Size and Power for a Specified Effect Size

Endpoint	N in Each Group	Baseline Rate	RR Detectable	Power*
Major Structural Defects**	75	3%	5.5 (6.1)	80% (84%)
Specific Pattern of 3 or more minor structural defects	75	1%	10.0	71%***
Spontaneous Abortion	85	10%	2.7 (3.0)	80% (88%)
Premature Delivery	75	10% (6%)	2.8 (4.0)	80% (85%)
Small for Gestational Age	75	10% (7%)	2.8 (3.5)	80%

***based on Fishers Exact Test, 2 tailed, alpha 0.05, except for specific pattern of three or more minor anomalies as noted below; normal approximation using Open Epi software**

****primary endpoint**

*****based on one-tailed Fishers Exact Test, alpha 0.05; power = 92% if two comparison groups are combined for n = 150**

The primary comparison group for all analyses will be the disease-matched unexposed comparison group. To the extent that there are not differences between the disease-matched and healthy comparison groups, these can be combined; however, based on previous experience with the OTIS Autoimmune Diseases in Pregnancy Project, for some endpoints (e.g. preterm delivery and reduced birth size) it may be inappropriate to combine control groups.

With respect to the evaluation of minor malformations, the strength of this study design is in the ability to examine the data for a pattern major structural defects and minor structural defects, given that the known human teratogens are typically associated with a pattern as opposed to isolated major birth defects. The baseline prevalence of a specific pattern of 3 or more minor structural defects is estimated to be essentially zero as the occurrence of the same three low baseline frequency minor structural defects in any two children in a sample of 75 would be an extremely unlikely random event. However, for purposes of the power calculation, a hypothetical baseline prevalence estimate of 1% has been used. The relative risk detectable with this sample size (10.0) is based on approximately 71% power, and an alpha of 0.05 using a 1 tailed Fishers Exact Test and 92% power to detect the same effect

size if the two comparison groups can be appropriately combined. This represents a 10% birth prevalence of a specific pattern (i.e., approximately 7 children in the exposed sample), which is comparable to the birth prevalence of a specific pattern in other known human teratogens of moderate risk such as the anticonvulsant medications.

8.6. Data management

9.6.1 Data sources, collection and validation

Data will be collected using interview, medical record, diary, and physical examination data. Data will be recorded on hard copies of forms and these records will be retained by OTIS. These forms are considered the primary data sources for the study. Data from these forms will be extracted and entered into a customized OTIS study database located in the Research Center and developed specifically for the OTIS studies.

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 study statistician also conducts reviews of the cumulative data from the study in the database for distributions and values that are illogical. The study manager will be responsible for working with the data manager and the supervisory staff to oversee the data validation procedures.

Access to the database will be controlled by password, with different access privileges assigned to the data entry staff and administrative staff; these privileges are outlined in detail in the OTIS Data Management Guide, Data Entry SOP, and supplements to these guides. An audit log is built into the database to archive all such entry edits. Hard copies of patient files and subject 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.

9.6.2 Data quality control

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 SOPs 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 primary study endpoint, verification of the outcome identified and classification is provided by blinded review by co-investigator, Kenneth Lyons Jones, MD.

9.6.3 Analysis software

R open source software is used for descriptive interim reports, and final analyses, as well as any *ad hoc* analyses as requested.

8.7. Data Analysis

- The primary population for analysis will be those enrolled in the prospective cohort study. Statistical analyses of those enrolled who do not meet the cohort study criteria will be descriptive only (Section 9.10). These cases constitute an exposure series, so tables of pregnancy characteristics, exposures and outcomes will be included in the interim and annual reports, and tabulations of the frequencies of events will be included by category of report: retrospective vs. prospective, reasons for exclusion, timing of exposure, and indication for use of the medication.
- Demographic and baseline characteristics will be compared between cohort study groups. Discrete variables will be compared between groups using chi-square tests or Fishers Exact test as appropriate.
- The primary analysis for the **primary** endpoint for the cohort study will be a comparison of the birth prevalence of major structural defects in live born infants between the apremilast-exposed group and the **primary** Comparison Group I. This analysis will use chi-square or Fisher's Exact test for univariate comparisons and logistic regression for adjustment of confounding. The primary analysis of the primary endpoint will be conducted at the end of the study.
- Statistical methods:
    - Using standard statistical software, crude comparisons will be made first between the apremilast-exposed group and primary (disease-matched) comparison group and then the secondary (non-disease) comparison group.
    - The primary comparison will be the proportion of all live born infants with a major structural defect identified up to one year of age, and the secondary comparison will the proportion of infants with a major structural defect identified among all infants with outcome (less lost-to-follow-up).
    - Crude comparisons will be made using chi-square or Fisher's Exact Test as appropriate. Crude comparisons will be made for the outcomes of spontaneous abortion and preterm delivery using survival analysis methods (e.g., Kaplan-Meier).
    - Crude comparisons will be made for the proportion of live born infants who are small for gestational age on weight, length or head circumference using chi-square or Fisher's Exact Test as appropriate.
    - The proportion of infants with 3 or more minor malformations, (among those who have received the dysmorphology examination) will be compared using chi-square or Fisher's Exact test, as will the proportion of infants with a specific pattern of minor malformations if any are identified in the apremilast-exposed group.

- Postnatal growth parameters will be compared using proportion of infants less than or equal to the 10th centile for sex and age with respect to weight, height or head circumference.
- The proportion of infants with serious opportunistic infections, hospitalizations, and malignancies identified up through one year of age will be compared using chi-square or Fisher's Exact test
- Results for categorical comparisons will be presented as point estimates of relative risk with 95% confidence intervals.
- Results for survival endpoints will be presented as cumulative rates with 95% confidence intervals.
- The primary analysis for the primary outcome will include adjustment for confounders using standard exact methods or logistic regression techniques, and for survival outcomes, using Cox proportional hazards methods.
- A propensity scoring approach for adjustment for confounding will be considered.

- External comparisons:
  - The overall rate/proportion of major structural defects will be compared to the most recently available rate/proportion from the MACDP.
- The evaluation for a pattern of defects will be conducted using the following steps:
  - A review of major structural defects will be made by category. A review of specific malformations will be conducted taking into consideration timing, dose, and biological plausibility.
  - Structural defects identified in aborted fetuses will be reviewed separately from the primary analysis. Pregnancy outcome in subjects who did not meet the study qualifying criteria (i.e., prior prenatal diagnosis of fetal abnormality, late gestational age, or retrospective cases) will also be reviewed separately.
  - A comparison among groups of the proportion of infants with any three or more minor structural defects will be made without regard to pattern
- Among infants with three or more minor defects, the apremilast-exposed group will be examined for evidence of a specific pattern of three or more defects in any two or more children. If such a pattern is identified, Control Groups I and II will be evaluated for any evidence of the same pattern.
- Inter-rater reliability:
  - There may be variability in the assessment of minor structural defects among the study dysmorphologists. This possibility will be addressed in three ways:
    - The participating dysmorphologist have been working with this study protocol in the existing OTIS Autoimmune Diseases in Pregnancy Project and have participated in group training and evaluation exercises. These reliability evaluations involve having examiners independently examine the same infant and comparisons of exam

results and measurements are made. These evaluation exercises will continue periodically throughout the duration of this Registry.

- If a pattern of minor defects is identified in the interim or final analysis of the study data, photographs of the infants exhibiting this pattern will be independently evaluated by other examiners, and if deemed necessary, affected children can be re-examined by one of the other dysmorphologists to ensure agreement.
- In previous studies involving the evaluation of minor structural defects, certain minor structural defects tended to be less reliably detected than others. This raises the possibility of missed identification of a pattern that includes one or more of those defects. If the interim or final analysis suggest that one or two minor defects occur substantially more frequently among exposed infants regardless of examiner, and among these children an additional defect or defects has been identified only by certain examiners, it may be necessary to have infants with those defects re-examined by a one of the other dysmorphologists.

- Losses to follow-up:
  - Prospectively reported pregnancies for which outcome information is unobtainable are considered "losses to follow up". It is possible that outcomes among pregnancies lost to follow up could differ from those with documented outcomes. Because of differences in follow-up and reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases the losses to follow up may have on any analysis of prospective case reports. Should loss to follow-up numbers be substantial, however, efforts at comparing some of the characteristics of each group are conducted in an attempt to address this potential source of bias. However, the OTIS Research Center experience has been that losses to follow-up are extremely low.
- Interim reports and termination of study:
  - The Registry will develop an Annual Report and any additional ad hoc reports with the advice of the Advisory Committee. Each report will be a composite of the cumulative data to date and will supersede any previous reports. Descriptive analyses may be presented. Descriptive analyses will be supportive. The study may be terminated at any time based on these findings. This decision will be considered and a recommendation made upon review by the Advisory Committee.

8.8. Quality control

Interview, medical record and examination data will be recorded on hard copies of forms and these records 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 HIPAA authorization that each subject will sign in order to receive medical record information. All records are maintained for a minimum of 10 years following study completion.

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

8.9. Limitations and strengths of the research methods

The primary limitation of a cohort study utilizing volunteer subjects is potential selection bias. The use of comparably selected controls in both groups will address this concern to some extent. However, women who agree to enroll in the cohort study may represent particularly high or low risk pregnancies (Johnson, 2001). However, the study results will be strictly generalizable to women fitting the profile of the sample of women who enroll.

Another limitation of the study design relates to the evaluation of spontaneous abortion rates. Rates of early spontaneous abortion, i.e., at 7-9 weeks post-LMP or less, will not be measured in a study that enrolls women after recognition of pregnancy. The study results with respect to spontaneous abortion will be limited to relative risk for late first-trimester and early second-trimester pregnancy loss.

Because early prenatal testing is so prevalent in the U.S. and Canada, it may be difficult to achieve adequate numbers of patients if all pregnancies with prior prenatal testing are excluded from the analysis. Therefore, the Registry 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, 2002) 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, 1999). The data analysis will address this by sub-analysis stratifying on use of prenatal testing.

The calculation of frequency of birth defects excludes fetal losses (spontaneous abortions, induced abortions, or fetal deaths) for which no birth defects have been detected as they may introduce a classification bias. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or birth defects. The Registry attempts to obtain information on 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 the primary endpoint of the study will be conducted among pregnancies ending in live birth, and a secondary analysis of the primary endpoint will include all pregnancies with known outcome.

It is expected that many exposures to apremilast will occur in unintended pregnancies. Although more than half of all pregnancies in the U.S. are unintended (Henshaw, 1998), the possibility of confounding by age, race, and other demographic variables will be considered. For example, the rate of unintended pregnancies is higher among low-income women/families than among the other socioeconomic groups. It is possible that demographic

variables will be associated with treatment as well. As such, these factors will be taken into consideration in the recruitment of comparison groups and in the analysis.

Another factor to be considered in a study anticipated to encompass a five-year recruitment period is the potential impact of changing trends in prescribing practices along with physician and maternal attitudes toward the use of apremilast in pregnancy. 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. In addition, as more post-marketing experience with the medication is accumulated, the number and characteristics of exposed pregnancies, the proportion electively terminated, and the length of exposure may change. These trends will need to be addressed in the analysis.

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 which may be related to exposure and to pregnancy outcome, and the use of a disease-matched comparison 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. In addition, each subject is interviewed at several predetermined intervals during pregnancy. Misclassification bias in outcome is minimized in this study design through the use of a specialized physical examination and a standardized evaluation protocol. Another strength of the study design is the anticipated minimal losses-to-follow-up rate. Based on previous experience of the investigators in the OTIS Autoimmune Diseases in Pregnancy Project and other similar studies, and the frequent subject contact, lost-to-follow-up is expected to be <5%, and therefore not expected to pose a threat to the validity of study results.

Finally, the small sample size that is projected to be achievable for this Registry has limitations in statistical power. However, the investigators and the Advisory Committee's expert review and comment on the data and the inclusion of evaluation of a pattern of major or minor anomalies is a strength.

8.10. Registry Case Report Management

The focus of the Registry will be the hypothesis-driven cohort study; however, the Registry will also function as a repository for case reports of exposures and outcomes that do not qualify for the cohort study. The management of these types of reports and how they will be analyzed is outlined in this section.

8.10.1. Sources of Participants

Pregnant women who do not qualify for the prospective cohort study may be self-referred to the Registry, come through health care providers, or come from the Sponsor's Safety group.

8.10.2. Patient Initiated Reports

Pregnant women who contact the Registry and who do not meet the criteria for the cohort study, for example, women who have already had prenatal diagnosis of a fetus with a major congenital defect or who contact the registry after 19 completed weeks' gestation following a first trimester apremilast exposure, or for whom the exposure to apremilast has only occurred in the father of the baby, will be consented, interviewed, medical records requested, and outcome examination will be performed using the same protocol as prospectively enrolled subjects in the cohort; however these subjects will not be included in the analysis for the cohort study. Women who contact the Registry with retrospective reports (reporting pregnancy outcome after pregnancy has been completed) will be consented, interviewed, medical records requested, and general pediatric evaluation requested utilizing the same protocol as subjects enrolled in the cohort; however, these subjects will not routinely be asked to participate in the dysmorphology examination portion of the study. Collection of exposure and outcome information will follow the same time schedule to the extent this can be achieved as set forth in the cohort study protocol (see Table 2).

Similar biases as noted in the cohort section 9.9 apply to prospectively ascertained case reports. In addition, these reports may be further biased by the very factors that excluded them from cohort eligibility. Retrospective case reports are thought to be subject to even further bias in that adverse outcomes may be more likely to be reported, and there is no known denominator of exposed persons. Therefore, rates of outcomes cannot be calculated from these data. However, a series of reported birth defects can be analyzed to detect patterns of specific birth defects and can identify early signals of therapy risks and can be evaluated in the context of any findings in the prospective cohort data.

8.10.3. Health Care Provider Initiated Reports

If the Registry is initially contacted by the health care provider, he or she will be asked to have the pregnant patient contact the Registry to provide informed consent and if the patient qualifies for the cohort study, she will be followed in that manner. If she does not qualify for the cohort study, but has had exposure to apremilast, she will be asked to enroll in the Registry exposure case series.

8.10.4. Sponsor Safety Surveillance or Pharmacovigilance

The Sponsor will provide the Registry with the number of reports of pregnancy exposures to apremilast received through the safety surveillance processes or studies in order to assist with evaluating potential for recruitment, and will encourage reporters to contact the Registry directly.

8.10.5. Reports from Published Literature

Relevant reports from the published literature will be included in the Registry Annual Report in the Appendices.

8.10.6. Information from Other Studies

As other data sources on pregnancy outcomes following maternal exposure to apremilast during pregnancy become available, they may be summarized and reported in the Registry Annual Report.

8.10.7. Recruitment/Awareness for Registry

Recruitment: Spontaneous referrals from OTIS member services will continue to be a major source of recruitment for the cohort study, especially for subjects who qualify for one of the two comparison groups. The existing OTIS Autoimmune Diseases in Pregnancy Project has utilized repeated direct mailing campaigns to provide information to health care professionals who are likely to treat pregnant women with an autoimmune disease. This strategy will be continued with the current Registry. In addition Registry staff will continue participation in scientific meetings of professional organizations to maintain relationships that have been established with referring physicians. In addition, members of the Advisory Committee will be asked to promote recruitment among colleagues. The existing Toll Free number for North American callers currently being utilized by the OTIS Autoimmune Diseases in Pregnancy Project (877-311-8972) will be maintained as a considerable amount of previous publicity for this number will enhance ease of contact for patients to the Registry.

Awareness: The existing OTIS Autoimmune Diseases in Pregnancy Project contact information is available on the web site dedicated to this project which will continue to function to maintain and increase awareness that this study is continuing (www.pregnancystudies.org). This study will be added to the FDA website for pregnancy registries (http://www.fda.gov/womens/registries/default.htm) and to Clinicaltrials.gov. This information will also be made available 1) in the prescribing information (package insert) for apremilast and other product literature and promotional materials, 2) via a link from the Celgene's web sites, and 3) in the Registry Annual reports. Additional venues for publicizing the Registry include: 1) linking the Registry web site to other rheumatology, dermatology, and maternal health interest web sites, 2) posting notices in appropriate journals or patient advocacy publications, and 3) later presenting Registry data at rheumatology, dermatology, and obstetrics-related scientific and clinical meetings. In addition, the Registry will enlist the aid of the FDA, CDC, The National Data Bank for Rheumatic Diseases, and other relevant organizations in facilitating patient recruitment, and the Sponsors will also provide information about the Registry at appropriate professional and patient advocacy meetings.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

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 laws.

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 both the UCSD IRB and Celgene 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 to allow the Registry to obtain information on the pregnancy and the pregnancy outcome from the patient's obstetrician healthcare provider, the hospital of delivery, and any healthcare specialist, and for the infant from the infant's pediatrician healthcare provider. 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 the University of California, San Diego and are compliant with HIPAA regulations.

9.2. Patient Withdrawal

Participants may withdraw from the study at any time at their own request, or they may 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 subject outcome, if possible. The Registry routinely inquires about and records the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the subject withdraws from the study, and also withdraws consent for collection of future information, no further data will be collected, but the Registry will retain and continue to use any data collected prior to the withdrawal of consent.

9.3. Institutional Review Board (IRB)

According to the FDA Guidance document, registries such as this must comply with ethical principles and regulatory requirements involving human subjects research. Therefore, this protocol and informed consent documents must be approved by the Institutional Review Board (IRB) at the University of California, San Diego. The chairman or the recording secretary of the IRB must have signed a form indicating approval. Notification of the Board's approval of the study must is provided to the Sponsor prior to initiation of participation in the Registry.

The Registry follows the FDA Guidance for Industry for regulatory reporting of SAEs to FDA. "The Agency considers pregnancy exposure registry reports (both prospective and retrospective) as derived from active solicitation of patient information." Therefore the Sponsor is responsible for "reporting any serious and unexpected events by regulatory definition and where a reasonable possibility exists that the drug or biological product caused the SAE within 24 hours" (FDA, 2002).

For FDA status reporting the Registry Interim Report can be appended to the submission as described in the FDA Guidance (FDA, 2002). The Annual Report contains the background, study design, and general analysis plan. It summarizes the study status and the cumulative data on the Registry to date. In addition, the Registry annual report contains individual line listings to assist the Sponsors in preparation of their submission. The Registry reports generated and line listings will be current to the most recent data cutoff period.

9.4. Ethical Conduct of the Study

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

10. MANAGEMENT AND REPORTING OF SERIOUS ADVERSE EVENTS

All specified serious adverse events as described below occurring in the apremilast-exposed group will be reported to the Sponsor on the FDA MedWatch form within 24 hours of the Registry becoming aware of the event. The specified events are: major birth defects, spontaneous abortion, stillbirth, elective termination, neonatal death, whether the event is expected, unexpected or attributed to apremilast. All other adverse events that are study endpoints are included in the annual and final report tables. Other adverse events that are not study endpoints are not actively solicited by the Registry; should a participant report such an event (e.g., a medication reaction) she will be referred to the Sponsor.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report describing the study endpoints will be prepared by the Registry and provided to the Sponsor. The Sponsor will communicate the results to the FDA.

Publications including manuscripts on the study outcomes will be prepared by the Registry Investigators and provided to the Sponsor. Manuscripts will be provided for comment at least 45 days in advance of planned submission. Abstracts and presentations will be provided for comment at least 7 days prior to planned submission.

The Registry will initiate presentations at scientific and professional meetings. The Registry will use these meetings and several other strategies to raise awareness of the Registry. However, the Registry never identifies individual subjects or shares its list of providers.

Interim Reports: An Annual Report will be issued to the Sponsor and the Advisory Committee on an annual basis in conjunction with the annual Advisory Committee meeting. Each issue will contain historical information as well as new data, and therefore will supersede all previous Reports. The Report will describe the experience of the ongoing study, summarize all reports to the Registry, and provide descriptive analysis of prospectively reported pregnancy outcomes in this Registry.

Web Site: Information on the Registry is incorporated into the existing OTIS website which includes a description of the Registry, contact information, enrollment eligibility and instructions. The FDA Pregnancy Registry web site will continue to list the OTIS Autoimmune Diseases in Pregnancy Project. There are other web sites that may provide Registry contact information. The Sponsors' web sites will maintain links to the Registry web site.
Abstracts, Manuscripts: The Registry Advisory Committee drafts policy for managing external requests for data analysis or use of information from the Annual Report. Data analyses to support these activities are conducted by the Registry Coordinating Center.

12. ADMINISTRATIVE CONSIDERATIONS

12.1.1. Responsibilities

12.1.1.1. Advisory Committee

An external Advisory Committee will be maintained by the Registry and will review all the Registry data on an ongoing basis, meeting on an annual basis to review the aggregate data. Members of the Committee provide advice to the Registry Investigators on interpretation of the data and provide advice on strategies for the dissemination of information regarding the Registry. An Annual Report is prepared after each meeting to summarize these aggregate data. The Advisory Committee is chaired by a designated member of the Committee. The Committee will meet at least annually.

12.1.1.2. Sponsor

The Sponsor provides financial support for the Registry and will support referrals to the Registry. The Sponsor will work with the Registry Investigators to ensure that objectives are being met, and that the Registry staff is assisting the Sponsor in meeting its regulatory reporting responsibilities. The Sponsor will be responsible for serious adverse event reporting to the regulatory authorities for their specific product.

12.1.1.3. Study Investigators and Research Coordinating Center

The Research Coordinating Center is responsible for the 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 Reports, and preparation of publications resulting from the Registry. In addition, the Coordinating Center schedules, plans, and conducts Advisory Committee meetings, and forwards reports of major birth defects, spontaneous abortions, stillbirths, elective terminations or neonatal deaths to the Sponsor within 24 hours of becoming aware of the event. The 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, as well as presenting results in abstracts and publications in scientific journals. The Coordinating Center is also responsible for communicating final results of the cohort study to the study participants.

The Project Investigators from the Coordinating Center are responsible for the conduct of the Registry. Project management activities include, managing the 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 the Sponsors and the Advisory Committee who will meet at least on an annual basis.

12.1.2. Disclosure of Data

12.1.2.1. Confidentiality

The Registry makes every effort to assure patient confidentiality within the Registry. When information on reports is distributed to Advisory Committee members, no health care provider contact information or direct patient identifiers are included. Contact information is not shared outside the Registry except with the Sponsors for regulatory safety surveillance purposes when reporting major birth defects, and then only with permission of the subject.

The patient and infant health information in summary form from the limited dataset of protected health information is shared with the Sponsor and the Advisory Committee, but is not reported in the Registry Annual Report or any other publications or presentations. The information includes dates of exposure, prenatal tests, LMP, and pregnancy outcome and other relevant assessment data.

Who Has Access to the Data

Registry Staff: The Registry Investigators, data collection and management staff reside at the OTIS Autoimmune Diseases in Pregnancy Project Coordinating Center located at the University of California, San Diego. These personnel, under the supervision of the Investigators, have access to the physical files and electronic data.

Sponsor: Sponsor representatives through the Registry Advisory Committee have access to de-identified summary data from the database as part of the periodic annual review. In addition, the Sponsor will comply with regulatory safety surveillance reporting and labeling update requirements. For this reason, any reports of SAEs (major birth defects, spontaneous abortions, elective terminations, stillbirths, and neonatal deaths) not originating at the Sponsor will be reported to the Sponsor through the MedWatch protocol by the Registry staff, as described previously, regardless of attribution. This data will be utilized by the Sponsor to meet the FDA reporting requirements.

Advisory Committee: The Registry Advisory Committee will receive information on pregnancy related serious adverse events occurring during the reporting period. Contact information is not included in any listings provided. The Advisory Committee, in preparation for the annual meeting, reviews the listings and summary tables. At the meeting, interpretation of results will be discussed and decisions made on the appropriate updates to the Annual Report.

Patient Identifiers: Mother and infant names are obtained as part of the informed consent and linked to pregnancy history, exposure and outcome data from maternal interview, medical records, and physical examinations. This personally identified information is maintained securely at the Coordinating Center and is not shared with the Sponsor, Advisory Committee, or any external parties other than what is required by law. Data summaries for the Sponsor and Advisory Committee will be provided only when data has been stripped of personal identifiers.

Published Data: Care is taken to assure that a patient is not identifiable in the data tables published in the Annual Reports, or other publications. No protected health information is included in any published information. Ad hoc requests for Registry information are reviewed and approved by the Registry Investigators with the advice of the Advisory Committee.

12.1.3. Discontinuation of the Registry

Discontinuation of the Registry will be considered at such time as:

- sufficient information has accumulated to meet the scientific objectives of the Registry, i.e., the target sample size is achieved
- other methods of gathering appropriate information become achievable or are deemed preferable, or
- the feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or losses to follow up.

The Registry Investigators and the Sponsor will notify the IRB and FDA of study discontinuation/termination. These considerations are documented in the FDA Guidance document (FDA, 2002).

If the Sponsor discontinues manufacturing apremilast, they may withdraw from the Registry upon written notification.

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14. LIST OF TABLES

APPENDIX 1. LIST OF SERIOUS OPPORTUNISTIC INFECTIONS UP THROUGH ONE YEAR INFANT FOLLOW-UP

Tuberculosis
X-ray proven pneumonia (requiring antibiotic treatment and/or hospitalization)
Neonatal sepsis
Meningitis (aseptic or culture proven)
Bacteremia
Invasive fungal infection (biopsy proven)
Pneumocystis
Septic arthritis
Osteomyelitis
Abscess (deep tissue)