SYNOPSIS

REGISTRY PROTOCOL

COMPOUND: Teriflunomide

STUDY NUMBER: OBS13499

STUDY NAME: Teriflunomide Pregnancy Outcome Exposure Registry: An OTIS Autoimmune Diseases in Pregnancy Project

VERSION DATE/STATUS: 12-February-2013/Approved

The Sponsor(s) is/are: Genzyme, a Sanofi company

NAMES AND ADDRESSES OF

STUDY MANAGEMENT

Name:
Address:

[redacted]

Tel:
Fax:
E-mail:

[redacted]

Name:

Address:

[redacted]

Tel:
Fax:
E-mail:

[redacted]

PHARMACOVIGILANCE

Company: Genzyme, a Sanofi company
Address:

[redacted]

Tel:
Fax:

[redacted]

SPONSOR	Company: Address: Tel: Fax:	Genzyme, a Sanofi company [redacted]
ADVISORY COMMITTEE CHAIRPERSON	Name: Address: Tel: Fax: E-mail:	[redacted]

TABLE OF CONTENTS

PROTOCOL AGREEMENT FORM

I, investigator, have examined this protocol for the registry_____

Entitled: Teriflunomide Pregnancy Exposure Registry: An OTIS Autoimmune Diseases in Pregnancy Project

Date:

And I have fully discussed the objectives of this registry and the contents of this protocol with the Sponsor's representative(s).

I agree to conduct the registry according to this protocol and to comply with its requirements, subject to ethical considerations.

I agree to keep confidential the content of the protocol, not to disclose it to any third party and to use it only for the purpose of conducting this registry.

I understand that, should the decision be made by the Sponsor to terminate prematurely or suspend the registry at any time for whatever reasons, such decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the registry I will communicate immediately such decision in writing to the Sponsor.

Investigator	**Sponsor**
NAME: [redacted]	[redacted]
SIGNATURE:	SIGNATURE:
DATE: _____	DATE: _____

1 SYNOPSIS

COMPOUND: **Teriflunomide** **STUDY No.:** OBS13499

Title	Teriflunomide Pregnancy Outcome Exposure Registry: An Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Project
Trial location	United States and Canada
Advisory Committee Chair	[redacted]
Objectives	Primary: To evaluate any potential increase in the risk of major birth defects, in the first year of life, in teriflunomide-exposed pregnancies. Secondary: To evaluate the potential effect of teriflunomide-exposure on other adverse pregnancy outcomes including any potential pattern of minor birth defects, spontaneous abortion, stillbirth, preterm delivery, small for gestational age at birth and at 1 year follow-up.
Study design & duration	This is a North American prospective, observational, exposure cohort study of pregnancy outcomes in women with multiple sclerosis (MS) who are exposed to teriflunomide during pregnancy. The outcomes in women exposed to teriflunomide will be compared to those observed in two comparison groups: one in women with MS who have not been exposed to teriflunomide during pregnancy, and the other in women without MS. This method was previously used for the leflunomide pregnancy exposure registry in rheumatoid arthritis conducted by the OTIS research group (Chambers et al, 2010). The overall duration of recruitment is planned for five years, with Registry initiation expected in April, 2013.
Population	The study population for the cohort study includes pregnant women with a confirmed diagnosis of MS and teriflunomide exposure during pregnancy (Cohort I), and 2 comparison groups that represent pregnant women without teriflunomide exposure during pregnancy. One comparison group (Cohort II) will consist of pregnant women with MS not exposed to teriflunomide during the current pregnancy. The secondary comparison group (Cohort III) will consist of healthy pregnant women who do not have a known diagnosis of MS and have no known exposure to a known human

teratogen

Recruitment is planned for a total of 325 subjects across all 3 cohorts from sites in the U.S. and Canada.

A. Cohort I: Teriflunomide-exposed pregnant women with MS

- Inclusion Criteria:

Pregnant women who have previously been treated with teriflunomide, including women who were treated during a clinical trial, who are participating in another registry, or who are treated with other approved disease modifying therapy for MS, 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).

  - Pregnant women who have provided an oral and/or written consent to enroll no later than 20 completed weeks from LMP.
  - Pregnant women who 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 (up to 1 year post birth).

- Exclusion Criteria:
  - Pregnant women with exposures commencing after the 12th week post-LMP.
  - Pregnant women who come in first contact with the project after prenatal diagnosis of a major structural defect.
  - Pregnant women who first come in contact with the project after 20 completed weeks' gestation.
  - Pregnant women who had previously enrolled in the study for a previous pregnancy (only 1 pregnancy, per woman, may be registered)
  - Retrospectively reported cases.

B. Cohort II – Pregnant women with MS not exposed to teriflunomide during the current pregnancy

- Inclusion Criteria:
  - Pregnant women with a diagnosis of MS who have:
    1. Not taken teriflunomide at any time but who may or may not have taken another medication for MS during the current

	pregnancy, or, 2. Previously been treated with teriflunomide within 2 years prior to the index pregnancy and have documented blood levels below 0.02 mcg/mL prior to pregnancy, or 3. Previously been treated with teriflunomide greater than 2 years prior to the index pregnancy • Pregnant women who have provided oral and/or written consent to enroll no later than 20 completed weeks from LMP. • Pregnant women who 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 (up to 1 year post birth). • Pregnant women can be taking any other approved disease modifying therapy for MS • Exclusion Criteria: • Pregnant women who come in first contact with the project after prenatal diagnosis of a major structural defect. • Pregnant women who first come in contact with the project after 20 completed weeks' gestation. • Pregnant women who had previously enrolled in the study for a previous pregnancy (only 1 pregnancy, per woman, may be registered). • Pregnant women who had previously been treated with teriflunomide if they had received any dose of the drug within 2 years prior to the index pregnancy and do not have documented blood levels below 0.02 mcg/mL prior to pregnancy. • Retrospectively reported cases. <u>C. Cohort III - Pregnant women without MS and not exposed to teriflunomide or any known human teratogen</u> • Inclusion Criteria: • Pregnant women who do not have a known diagnosis of MS and have no known exposure to a known human teratogen, as determined by the referring Teratogen Information Specialists and confirmed by the OTIS Research Center. • Pregnant women who have provided oral and/or written consent to enroll no later than 20 completed weeks from LMP.

	• Pregnant women who 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 (up to 1 year post birth).
	• Exclusion Criteria:
	  • Pregnant women who first come in contact with the project after 20 completed weeks' gestation.
	  • Pregnant women who first come in contact with the project after prenatal diagnosis of a major structural defect.
	  • Pregnant women who had previously enrolled in the study for a previous pregnancy (only 1 pregnancy, per woman, may be registered).
	  • Retrospectively reported cases.

Recruitment modalities	The registry cohort study will be conducted by the OTIS Research Group with recruitment supported by the Organization of Teratology Information Specialists (OTIS), an academic network of university and health department-based telephone information centers serving pregnant women and health care providers throughout the U.S. and Canada. All exposed subjects and comparison subjects will be recruited through spontaneous callers to participating OTIS member services in locations throughout North America who will contact the study center located in the U.S. using a toll-free number available in the U.S. and Canada, and through active recruitment strategies, e.g., direct mailings to neurologists and obstetricians/gynecologists, website, the registry study referenced on FDA website, Clinicaltrials.gov website, product website, neurology and maternal health interest websites and on the information document provided to the patients at time of dispensing the drug (such as medication guide, patient information leaflet), and professional journals and meetings.
Main evaluation criteria	Comparison of the pregnancy outcomes in women exposed to teriflunomide for the treatment of MS, with those observed in women with MS who have not been exposed to teriflunomide during pregnancy, and to the pregnancy outcomes of women without MS.
Main data collected	During Pregnancy: • history of previous pregnancy outcomes • health and family medical history including history of MS disease • socioeconomic and demographic information including maternal and paternal age, occupation, education, race/ethnicity

	• pre-pregnancy maternal body mass index • course of current pregnancy including prenatal tests • exposure type, dates and dosages during the current pregnancy including all MS medications, other medications including over-the-counter and prescription products, vitamin and mineral supplements, vaccines, illness, fever, procedures • blood levels of teriflunomide and dates, courses of drug elimination procedures and dates • measures of disease activity/severity during pregnancy, age at diagnosis Pregnancy and Birth Outcomes: • the outcome of pregnancy • gestational age, sex of infant(s), delivery type, including cesarean section, length and type of hospital stay, maternal and infant complications • maternal weight gain • Apgar scores • major structural defects • birth weight, length and head circumference • method of infant feeding • pathology results, if relevant Postnatal Outcomes for Live Born Infants: • Physical examination by one of a team of study pediatricians who are dysmorphologists/geneticists for both major and minor structural anomalies in first year of life, as well as growth • Growth and development within 6 months of delivery and at 1 year of age evaluated by general pediatrician
Statistical methodology	• The primary analysis variable is rate of major structural defects in live born infants in the first year of life. • The group comparisons will be carried out using Fisher's exact test. Multivariate analysis, adjusting for confounders, will be conducted where feasible. • The secondary analysis variables include proportion of major

	structural defects in all pregnancies excluding lost-to-follow-up, proportion of a specific pattern of 3 or more minor structural defects in the live born infants, the incidence of spontaneous abortion, stillbirth, preterm delivery, small-for-gestational age at birth, and small-for-gestational age at 1 year. • Except spontaneous abortion and preterm delivery, the secondary analysis variables will be analyzed in the same fashion as major structural defects, with the exception that the Chi-squared test will be used for comparison between the exposed and the comparison group when the events are not rare. For spontaneous abortion and preterm delivery, a survival analysis incorporating left truncation will be conducted. • The primary comparison group for the teriflunomide exposed cohort is the MS disease-matched cohort. • The secondary comparison group is the healthy cohort. • Sample size is set at 75 in the teriflunomide-exposed cohort and 125 in each of the comparison cohorts. With this sample size, at 80% power and 2-sided significance level of 0.05, using Fisher's exact test we will be able to detect a relative risk of 5.57 for proportion of major structural defects in the teriflunomide-exposed group versus the disease-matched comparison group, which has an assumed major structural defect rate of 3%.
Timelines	The Registry study will be open for enrollment upon FDA review and approval. Registry initiation is anticipated to be April 2013. Enrollment will open in Canada upon approval of teriflunomide by Health Canada. The duration of enrollment is expected to be approximately 5 years in the United States and approximately 4 years in Canada. The last pregnancy will then be followed for up to 1 year post delivery.

2 LIST OF ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
EDD	Estimated Date of Delivery
FDA	Food and Drug Administration
GEP	Good Epidemiological Practices
HCP	Health Care Provider
HIPAA	Health Insurance Portability and Accountability Act
ICSR	Individual Case Safety Report
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
MS	Multiple sclerosis
SAE	Serious Adverse Event

3 INTRODUCTION AND RATIONALE

3.1 BACKGROUND

The majority of individuals who are diagnosed with multiple sclerosis (MS) are women of childbearing age. Data suggest pregnancy course and birth outcomes among women with MS who deliver live born infants are generally similar to those of women without MS (Tsui & Lee, 2011; Nelson & Ostensen, 1997; Jalkanen et al, 2010)(1)(2)(3). However, the use of immunomodulatory and immunosuppressive drugs to treat MS, as well as other potential confounding factors such as variation due to unplanned pregnancies (e.g., failure to take periconceptional folic acid supplements, discontinue alcohol and tobacco use, etc.) may have an impact on pregnancy outcomes. Thus, although maternal disease itself is not known to be a risk, it has not been comprehensively studied. In the context of a medication exposure, it is critical to control for the contribution of the maternal disease as well as comorbidities and other exposures that may contribute to pregnancy risk.

3.2 RATIONALE

The purpose of the Teriflunomide Pregnancy Outcome Exposure Registry study is to monitor pregnancies in women with MS exposed to teriflunomide, in order to evaluate the possible teratogenic effects of this medication on the pregnancy outcome. The lack of sufficient human fetal safety data for teriflunomide makes such a monitoring system an important component of epidemiologic research on the safety of this drug. In addition, the purpose of the registry study is to serve as an educational resource for clinicians who prescribe teriflunomide and to women of reproductive age who are taking teriflunomide.

3.2.1 Cohort study potential biases, limitations and strengths

The primary limitation of a cohort study utilizing volunteer subjects is selection bias (Honein et al, 1999)(4). 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. However, the study results will be strictly generalizable to women fitting the profile of the sample of pregnant women who enroll.

Because early prenatal testing is prevalent in the US and Canada, it may be difficult to achieve adequate numbers of patients, if all pregnancies with prior prenatal testing were excluded from the analysis. Therefore, the registry cohort study will include pregnancies, enrolled prior to outcome, but after a prenatal test, as long as the test does not indicate a fetus with a major structural defect. The FDA guidance document, "Guidance for Industry, Establishing Pregnancy Exposure Registries" dated August, 2002(5) acknowledges that such an approach may be necessary to accrue adequate numbers. However, this practice could potentially bias the results by lowering the overall birth prevalence of birth defects among

those with normal prenatal test results. The data analysis will address this by stratifying use of prenatal testing prior to enrollment.

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 study 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.

It is expected that virtually all exposures to teriflunomide will occur in unintended pregnancies. More than half of all pregnancies in the U.S. are unintended, (Henshaw, 1998)(6) and this may lead to age, race, and other biases in the sample. For example, the rate of unintended pregnancies is higher among low-income women/families than among the other socioeconomic groups (Finer & Zolner, 2011)(7). Data on intendedness of pregnancy is collected as part of the study interview from all mothers. These factors will be taken into consideration in the recruitment of comparison groups and in the analysis.

The study design has relative strengths with respect to the ability to control for 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 lost-to-follow-up rate. Based on previous experience of the investigators in the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy Project and other similar studies, and the frequent subject contact, lost-to-follow-up is not expected to pose a threat to the validity of study results.

Finally, the primary strength of the cohort study portion of the pregnancy registry study is its sensitivity for detection of a pattern of malformation. As the 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 (Chambers et al, 2001)(8).

4 STUDY OBJECTIVES

The objectives of this cohort pregnancy registry study are to estimate the risk of birth defects and other adverse pregnancy outcomes occurring in offspring of women exposed to teriflunomide during pregnancy, and to detect any increase in the prevalence or pattern of these outcomes among exposed pregnancies. Determination of risk in the teriflunomide exposed group will be based on a primary comparison to a disease-matched group and a secondary comparison to a non-disease control group. Structural defects will be classified according to external data from a population-based birth defects surveillance program (The Metropolitan Atlanta Congenital Defects Program [MACDP])(9).

4.1 PRIMARY OBJECTIVE

To evaluate any potential increase in the risk of major birth defects in the first year of life, in teriflunomide-exposed pregnancies.

4.2 SECONDARY OBJECTIVES

To evaluate the potential effect of teriflunomide exposure on other adverse pregnancy outcomes including any potential pattern of minor birth defects, spontaneous abortion, stillbirth, preterm delivery, small for gestational age at birth and at 1 year follow-up.

5 DESCRIPTION OF THE STUDY

5.1 DEFINITION OF THE DISEASE

Multiple sclerosis (MS) affects approximately 1 in 800 people and is characterized by inflammatory lesions affecting the brain and spinal cord, causing neurological disability. In most patients, the disease initially follows a relapsing-remitting course. Some individuals have a more progressive form of the disease. The pathogenesis of the disease is not clearly understood, but like many autoimmune disorders, the majority of individuals who are diagnosed with MS are women of childbearing age (Tsui & Lee, 2011; Nelson & Ostensen, 1997; Jalkanen et al, 2010)(1)(2)(3). The purpose of the Teriflunomide Pregnancy Outcome Exposure Registry is to monitor pregnancies in women with MS exposed to teriflunomide in order to evaluate the possible teratogenic effects of this medication on the pregnancy outcome, while accounting for the potential contribution of the disease itself to adverse pregnancy outcomes.

5.2 DESCRIPTION OF THE STUDY DESIGN

This is a North American prospective, observational, exposure cohort study of pregnancy outcomes in women with MS who are exposed to teriflunomide during pregnancy. The outcomes in women exposed to teriflunomide (Cohort I) will be compared to those observed in 2 comparison groups: 1 comparison group of women with MS who have not been exposed to teriflunomide during pregnancy during the current pregnancy (Cohort II), and the other comparison group of healthy women without MS (Cohort III). This method was previously used for the leflunomide pregnancy outcome exposure study in rheumatoid arthritis conducted by the OTIS research group (Chambers et al, 2010)(10). The Teriflunomide Pregnancy Outcome Exposure Registry cohort study will be conducted by the OTIS Research Group with recruitment supported by OTIS, a network of university and health department based telephone information centers serving pregnant women and health care providers (HCP) throughout the U.S. and Canada (Leen-Mitchell et al, 2000)(11).

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 neurologists and obstetricians/gynecologists, website, the registry study referenced on the FDA website, Clinicaltrials.gov, product website, neurology and maternal health interest websites and on the information provided to the patients at time of dispensing the drug (such as medication guide, patient information leaflet), and professional journals and meetings. Once women are in contact with the OTIS Research Center, enrollment in the pregnancy registry study is voluntary and requires informed consent of the pregnant woman. The registry study encourages enrollment as early in the pregnancy as possible, before any prenatal testing results are known.

5.3 DURATION OF THE STUDY

The total duration of the study begins with the first patient in and ends when approximately 325 patients are enrolled and followed up to 1 year post delivery. This study enrollment period is expected to be 5 years. The anticipated recruitment numbers by cohort by year are shown in Table 1, and are based on 1)experience with recruitment for leflunomide, and 2)expected higher pregnancy rate in MS patients. The start date for the registry is anticipated to be April 2013.

Table 1 - Recruitment timetable

Cohort	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Cohort I: Teriflunomide-exposed MS Women	10	20	20	20	5	75
Cohort II: MS Women	20	30	30	30	15	125
Cohort III: Healthy Women	20	30	30	30	15	125
Total	50	80	80	80	35	325

5.4 EVALUATION CRITERIA

Primary evaluation criteria:

The primary outcome of the cohort study is the birth prevalence of major structural defects recognized within the first year of life. The frequency of major structural defects will be ascertained in each of the 3 cohorts by maternal report, by medical record review, by the 1-year general pediatric evaluation, and by physical examination of live born infants by a study dysmorphologist/geneticist. Major structural defects will be classified according to the MACDP coding criteria (Centers for Disease Control and Prevention, 1998)(9).

The primary comparison group for the teriflunomide-exposed Cohort I is the MS disease-matched Cohort II. The secondary comparison group is the healthy comparison group, Cohort III. A tertiary comparison for the proportion of major structural defects will be made to the external comparison reference, the MACDP most recently published major defect rate (MMWR, 2008)(12).

Secondary evaluation criteria:

The secondary outcomes of the cohort study include the prevalence of a pattern of minor structural defects that does not occur in either of the comparison cohorts (Chambers et al, 2001)(8), the incidence of spontaneous abortion, stillbirth, preterm delivery and small-for-gestational age birth size and small for age postnatal growth measurements (less than or equal to the 10^{th} percentile for sex and age on weight, length or head circumference). The frequency of spontaneous abortion, stillbirth, preterm delivery and small for gestational age infants will be ascertained in each of the 3 cohorts by maternal report, by medical record review, by the 1-year general pediatric evaluation, and by physical examination of live born infants by a study dysmorphologist/geneticist. The frequency of minor malformations will be ascertained by the blinded physical examination of live born infants performed in the first year of life by a study physician, and will be classified using the study standard checklist of minor malformations (Chambers et al, 2001)(8).

6 STUDY POPULATION AND SELECTION OF PATIENTS

6.1 SAMPLE SIZE AND STUDY TIMETABLE, FOR THE COHORT STUDY

It is planned to recruit 325 pregnant women. Recruitment goals are set at 75 in the exposed group (Cohort I), and 125 in each of the other 2 comparison groups (Cohorts II and III). The sample size target was selected as realistic based on experience with recruitment in previous pregnancy registries, and the expectation that with effective labeling medication guidance, few pregnancies will occur with inadvertent exposure to teriflunomide, as has been the case with leflunomide. Given the limitations of the sample size in teriflunomide-exposed, a somewhat larger target sample size was selected for the 2 comparison groups to improve statistical power, as the pool of available subjects meeting the inclusion criteria for these 2 groups is much larger.

Study enrollment will be for 5 years. Enrollment will begin in Canada once teriflunomide is approved by local authorities.

6.2 ELIGIBILITY CRITERIA

Eligibility for the study includes the following:

- Residence in the U.S. or Canada at the time of enrollment
- Currently pregnant woman

6.2.1 Inclusion criteria for the cohort study

Cohort I: Teriflunomide-exposed pregnant women with MS

- Pregnant women who have previously been treated with teriflunomide, including women who were treated during a clinical trial, who are participating in another registry, or who are treated with other approved disease modifying therapy for MS, 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 LMP.
- Pregnant women who have provided an oral and/or written consent to enroll no later than 20 completed weeks from LMP.
- Pregnant women who 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 (up to 1 year post birth).

Cohort II – Pregnant women with MS not exposed to teriflunomide during the current pregnancy

- Pregnant women with a diagnosis of MS who have:
    1. Not taken teriflunomide at any time but who may or may not have taken another medication for MS during the current pregnancy, **or**
    2. Previously been treated with teriflunomide within 2 years prior to the index pregnancy and have documented blood levels below 0.02 mcg/mL prior to pregnancy, **or**
    3. Previously been treated with teriflunomide greater than 2 years prior to the index pregnancy
- Pregnant women who have provided oral and/or written consent to enroll no later than 20 completed weeks from LMP.
- Pregnant women who 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 (up to 1 year post birth)
- Pregnant women can be taking any other approved disease modifying therapy for MS

Cohort III - Pregnant women without MS and no exposure to any known human teratogen

- Pregnant women who do not have a known diagnosis of MS and have no known exposure to a known human teratogen, as determined by the referring Teratogen Information Specialists and confirmed by the OTIS Research Center.
- Pregnant women who have provided oral and/or written consent to enroll no later than 20 completed weeks from LMP.
- Pregnant women who 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 (up to 1 year post birth).

6.2.2 Exclusion criteria for Cohort Study

Cohort I: Teriflunomide-exposed pregnant women with MS

- Pregnant women with exposure to teriflunomide commencing after the

  12th week post-LMP.
- Pregnant women who come in first contact with the project after prenatal diagnosis of a major structural defect.
- Pregnant women who first come in contact with the project after 20 completed weeks' gestation.

- Pregnant women who had previously enrolled in the study for a previous pregnancy (only 1 pregnancy, per woman, may be registered).
- Retrospectively reported cases.

Cohort II: Pregnant women with MS not exposed to teriflunomide during the current pregnancy

- Pregnant women who come in first contact with the project after prenatal diagnosis of a major structural defect.
- Pregnant women who first come in contact with the project after 20 completed weeks' gestation.
- Pregnant women who had previously enrolled in the study for a previous pregnancy (only 1 pregnancy, per woman, may be registered).
- Retrospectively reported cases.
- Pregnant women who had previously been treated with teriflunomide if they had received any dose of the drug within 2 years prior to the index pregnancy and do not have documented blood levels below 0.02 mcg/mL prior to pregnancy.

Cohort III: Pregnant women without MS and no exposure to any known human teratogen

- Pregnant women who first come in contact with the project after 20 completed weeks' gestation.
- Pregnant women who first come in contact with the project after prenatal diagnosis of a major structural defect.
- Pregnant women who had previously enrolled in the study for a previous pregnancy (only 1 pregnancy, per woman, may be registered).
- Retrospectively reported cases.

6.3 MODALITIES OF RECRUITMENT

All exposed subjects and comparison subjects will be recruited through spontaneous calls to participating OTIS member services locations throughout North America, and through active recruitment strategies, e.g., direct mailings to neurologists, obstetricians, web site, Clinicaltrials.gov website, professional meetings, and the Sponsor's Call Center. Each OTIS service representative 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 representative will explain the study protocol to potentially eligible participants, and then will request permission to refer the woman to the registry study, enrolling at the University of California, San Diego. Potential subjects who agree to be referred will be contacted by the OTIS registry study staff or will be

given information to initiate contact themselves if they prefer. OTIS member services will also refer callers, to the registry study, for those women whose exposure to teriflunomide does not appear to qualify for the cohort study (e.g., first contact after 20 completed weeks gestation, repeat pregnancies, or retrospective reports), as these will be handled as Registry Case Reports (See Section 10.3).

6.3.1 Investigator selection

The Principal Investigator and Co-Investigators for this study were selected for their expertise in teratology, experience in conducting pregnancy outcome research related to human teratogenicity, experience in leading collaborative research studies, including pregnancy registries, and experience specifically in designing and implementing pregnancy registry study designs that involve internal control groups.

6.3.2 Participant selection

Women who may meet the inclusion and exclusion criteria for the study are referred to the OTIS Research Center by OTIS referral sites, by clinician referral, by self-referral, or other sources such as the Sponsor's Call Center. Women are screened at the OTIS Research Center for inclusion and exclusion criteria. Women who meet the criteria and are interested in participating in the study are administered oral informed consent by trained OTIS Research Center staff, prior to the first maternal telephone interview. Subsequently, signed informed consent and Health Insurance Portability and Accountability Act (HIPAA) consent are obtained from all enrolled women either via mail, or in-person, at the time of the physical examination. Women who do or do not meet the criteria for enrollment following teriflunomide exposure will be offered referral information for laboratories where blood levels of teriflunomide can be measured and information about the drug elimination procedure will be provided.

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

7 STUDY PROCEDURES AND DATA COLLECTION

7.1 VISIT SCHEDULE

Table 2 - Timing of cohort enrollment, interviews, examinations, medical records

	<20 weeks' gestation	16-20 weeks' gestation	26-32 weeks' gestation	0-6 weeks after delivery	0-6 months after delivery	1 year after delivery
Referral	X					
Enrollment and Consent	X					
Intake Interview	X					
Interim Interview I		X				
Interim Interview II			X			
Outcome Interview				X		
Medical Record Review					X	
Dysmorphological Examination						X
Pediatric Medical Record Review and Questionnaire at 1 Year						X

*outcome interview and medical record review will be performed within 6 weeks and 6 months respectively following the end of pregnancies that result in spontaneous abortion, elective termination or stillbirth.

7.2 DATA COLLECTED FROM THE MOTHER

Following oral administration of informed consent, a structured maternal intake telephone interview will be conducted by a trained Research Associate at OTIS. This interview will include questions as itemized below and information will be updated at all subsequent maternal interviews. Women who have had teriflunomide exposure will be informed that teriflunomide serum levels and elimination procedures can be arranged through their health care provider and/or the teriflunomide patient management program.

Following the initial intake interview, participants will be sent a pregnancy diary on which they will be asked to record any additional exposures or events as the pregnancy progresses. Women 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 6 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 6 weeks after expected due date (see

Table 2). 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. The maternal outcome interview will be conducted within approximately 4 weeks of the end of the pregnancy.

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

During Pregnancy:

- History of previous pregnancy outcomes
- Health and family medical history including history of MS disease
- Socioeconomic and demographic information including occupation, education, race/ethnicity of mother and father, and family income category
- Course of current pregnancy including prenatal tests, test results, pre-pregnancy body mass index
- Exposures during the current pregnancy including over-the-counter and prescription medications including all treatments for MS, vitamin supplements, herbal products, tobacco, alcohol, illicit drugs, occupational and environmental exposures
- Dosage and dates of teriflunomide
- Cholestyramine or charcoal elimination procedure(s), dates and compliance
- If blood levels for teriflunomide were measured, dates and results
- Measure of MS disease severity/activity

At Completion of Pregnancy:

- The outcome of pregnancy
- Gestational age at pregnancy end
- Sex of the infant (s)
- Delivery type
- Type of hospital stay
- Maternal and infant complications
- Maternal weight gain
- Major structural defects,
- Birth weight, length, head circumference
- Apgar scores
- Method of infant feeding

- Additional medications or tests since last interview

7.2.1 Site / Investigator questionnaires

Not Applicable.

7.2.2 Screening log

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

7.2.3 Data Collected from medical records

Medical records from the prenatal care provider, the hospital of delivery, the neurologist, the pediatrician, and any other specialty provider such as a pathologist, if relevant, will be examined for additional exposure and outcome data. Upon completion of the outcome interview, regardless of the outcome of the pregnancy, each woman will be mailed a packet containing medical records release forms for the delivery hospital, obstetrician, pediatrician, and neurologist if applicable, as well as the laboratory results, if blood levels of teriflunomide were obtained at any time point during or just prior to pregnancy and documentation of courses and dates of the drug elimination procedure. Each woman will be asked to sign the medical records release forms and to return them 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 the physician responsible for the care of each live born infant at or near 1 year of age. 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.

Data abstracted from the medical records include the following:

- Prenatal tests and results
- Measures of disease activity/severity during pregnancy, age at diagnosis
- Blood levels of teriflunomide and dates measured (if available)
- Courses of cholestyramine or charcoal prescribed and dates
- Outcome of pregnancy
- Gestational age at pregnancy end
- Sex of the infant (s)
- Delivery type
- Type of hospital stay
- Maternal and infant complications

- Maternal weight gain, pre-pregnancy body mass index
- Major structural defects, and any diagnostic tests to confirm
- Birth weight, length, head circumference
- Postnatal weight, length, head circumference
- Apgar scores
- Method of infant feeding
- Pathology results, if relevant, e.g., for stillbirths

7.2.3.1 Data collected from the dysmorphology examination

- Live born infants in all cohorts will be examined by 1 of 5 study dysmorphologists/geneticists. These study-specific health care providers who are performing the dysmorphology examination for minor malformations are highly qualified experts, trained specifically to perform the blinded infant evaluations.
- The physical examination of these infants includes evaluation of both major and minor structural defects, which will provide increased sensitivity for detecting the presence of specific patterns of malformation. All live born infants will be examined, to the best extent possible, within the first year of life. The OTIS registry study staff will group and schedule these follow-up examinations with study families, typically in the participant's home. These are scheduled 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 minor malformations included in a standard physical evaluation form. In addition, digital photographs of the infant's face will be taken to aid in validating any diagnoses.
- Dysmorphologists/geneticists will perform these examinations blinded to the exposure or control group status of the mothers. Because subjects with MS may have visible evidence of the disease, the use of a disease-matched control group allows for preservation of physician blinding.
- Data collected from these evaluations include:
  - Presence or absence of 1 or more of ~130 minor structural defects on the standard checklist
  - Presence of any major structural defect
  - Length and head circumference
  - Infant photographs

7.2.3.2 Outcome classification for structural defects for cohort study

The method for classifying structural defects for purpose of analysis has been previously described by the study investigators and the OTIS Research Group and has been used in previous studies conducted by this group, including the current OTIS Autoimmune Diseases in Pregnancy Project (Chambers et al, 2001; Chambers et al, 2010; Centers for Disease Control and Prevention, 1998)(8)(10)(12).

7.2.3.3 Classification of major and minor 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). The CDC's MACDP coding manual for major structural defects will be used as a guide for categorization. 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).
- Time period for identification: structural defects identified up to 1 year of age in the dysmorphological examination or the medical record will be included in the analysis.
- Categorization of defects: Defects identified in pregnancies ending in live birth will be considered in the primary analyses; data will be collected on defects occurring in pregnancies that end in spontaneous abortion, stillbirth and elective termination and these will be considered in secondary analyses.
- All definite and possible major structural defects reported in any study subject are reviewed by the lead study dysmorphologist, for classification and coding. A secondary level of review is provided by the Scientific Advisory Board members with expertise in this area.

7.2.3.4 Outcome classification for secondary endpoints for cohort study

- Pattern of minor structural defects is defined as any 2 or more infants receiving the study dysmorphology examination in the teriflunomide-exposed cohort (Cohort I) who have the same 3 or more minor structural defects. If a pattern or patterns are identified, the prevalence of the same pattern in Cohorts II and III is evaluated.
- Spontaneous abortion: spontaneous abortion is defined as non-deliberate fetal death which occurs prior to 20 completed week's 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 completed week's post-LMP.
- Premature delivery: premature delivery is defined as live birth prior to 37 completed weeks gestation as counted from LMP (or calculated from first-trimester ultrasound-derived due date if last menstrual period uncertain or more than 1 week discrepant).

Elective cesarean 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 10th percentile for sex and gestational age using National Center for Health Statistic (NCHS) pediatric growth curves for full term infants. Prenatal growth curves will be used for premature infants.
- Postnatal growth deficiency up to 1 year of age: 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: 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 a standard number of telephone attempts and attempt 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.

7.3 PROCEDURE FOR WITHDRAWAL OF PATIENTS FROM STUDY FOLLOW-UP SCHEDULE

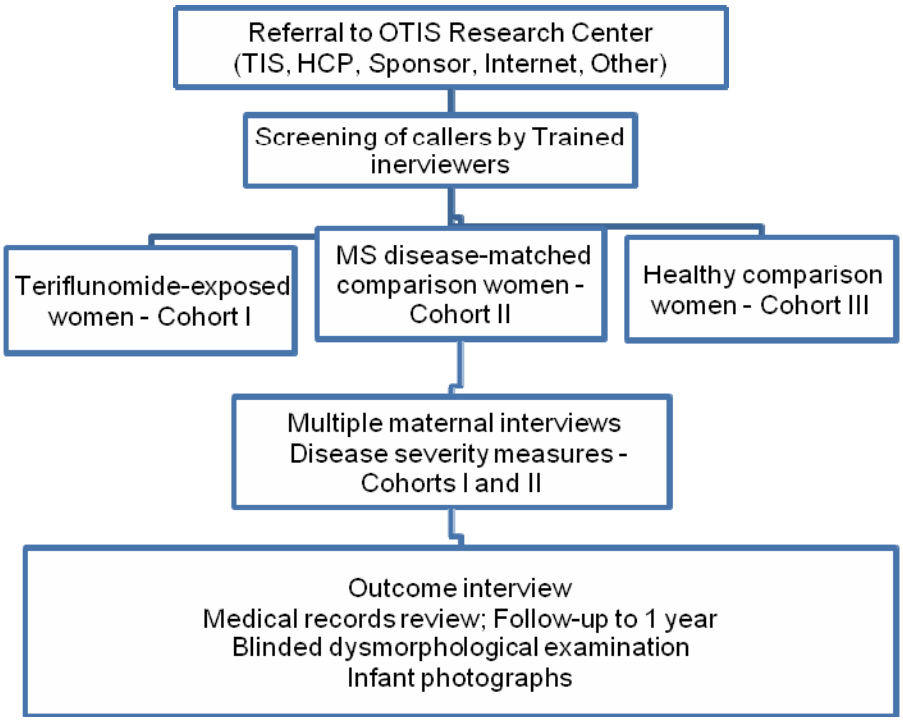
Participants, who meet the study criteria, consent to participation, and complete the intake interview will be considered enrolled. Every effort will be made by the OTIS Research Center Staff to complete all study visits as scheduled, and to collect outcome interview, medical records, and physical examination data. Subjects who do not complete the outcome interview following the end of the pregnancy will be considered lost to follow-up. Multiple attempts will be made to contact participants by telephone, mail, email, up to 1 year past the expected due date before a subject is deemed lost. Subjects who decline to complete participation after enrollment will be considered to have withdrawn consent and information collected on reasons for withdrawal. The statistical analysis plan will specify how these patients for whom outcome information is not available for study endpoints will be considered.

7.4 LOGISTIC ASPECTS

The OTIS Research Center maintains a national (U.S. and Canada) toll-free number, staffs this number during business hours, and is set up to take telephone messages after business hours. Participating OTIS referral sites screen for potential study candidates and obtain permission to refer to the OTIS Study Center. In addition, women may learn about the study through their health care provider, the web, or other media and promotional activities. Health care providers can learn about the study at Scientific Meetings where OTIS exhibits and/or presents information. The website describes the OTIS organization, the study objectives, and provides multiple modalities through which potential participants or health care providers can contact the OTIS Research Center to obtain more information. In all cases, however, once

screened, an eligible participant is the woman herself, and she is the person who must provide informed consent.

Figure 1: Study flow diagram



8 STATISTICAL METHODOLOGY

This section provides specifications for preparation of final statistical analysis plan (SAP), which will be issued prior to final database lock at the end of the study. Any differences compared to this statistical section should be identified and documented in final SAP. All interim annual study reports as described in Section 9 will provide descriptive data only. Statistical analysis will not be performed until the cohort study has been completed. Additional data on exposed pregnancies that do not qualify for the cohort study, as described in Section 10.5, will be included in interim and final reports using descriptive statistics only.

8.1 ANALYSIS POPULATION

This study consists of 3 cohorts recruited from the United States and Canada. The exposed group (Cohort I) consists of pregnant women with a confirmed diagnosis of MS and

teriflunomide exposure at anytime from the 1st day of LMP up to and including the 12th week after the first day of the LMP. The diseased comparison group (Cohort II) consists of pregnant women with a confirmed diagnosis of MS who have not been exposed to teriflunomide during the current pregnancy. The healthy comparison group (Cohort III) consists of pregnant women who do not have MS and have no known exposure to any known teratogen or teriflunomide. Participants who are deemed lost-to-follow-up or who withdraw before the known outcome of pregnancy (Section 7.3) will be reported in descriptive tables in all interim and final reports, but will be excluded from statistical comparisons.

8.2 ANALYSIS VARIABLES

The primary analysis variable is proportion of live born infants with a major structural birth defect within the first year of life and the secondary analysis variables: proportion of major structural defects in all pregnancies, proportion of infants with a pattern of 3 or more specific minor anomalies, the incidence of spontaneous abortion; stillbirth; preterm delivery; small-for-gestational age on birth weight, length, head circumference; small for age at 1 year follow-up on weight, length or head circumference.

Additional analysis variables that may or may not be included as important confounders or in sub-analyses include but are not limited to the following:

- Maternal age
- Maternal race/ethnicity
- Socioeconomic status
- Prior pregnancy history: gravidity/parity and previous outcomes
- Periconceptional use of folic acid containing supplements
- Unintended pregnancy
- Gestational age at enrollment
- Exposure to other medications (including known teratogens) and other MS medications
- Comorbidities
- Disease severity measure (s)
- Dose and gestational timing of exposure to teriflunomide
- Gestational timing and course of cholestyramine elimination
- Blood levels of teriflunomide if performed in pregnancy

8.2.1 Main criteria

The primary interest is the birth prevalence of major structural defects, in the first year of life, in the teriflunomide-exposed group.

As defined in Section 7.2.3.3, 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). The CDC's MACDP coding manual for major structural defects will be used as a guide for categorization of such defects.

The primary comparison group is the MS disease-matched Cohort II. The secondary comparison group is Cohort III. The additional external comparison will be made to the MACDP birth defects rate.

8.2.2 Other criteria

Other interests are the major structural defects in all pregnancies (refer to Section 7.2.3.3 for definition), the prevalence of a specific pattern of 3 or more minor structural defects in the live born infants who receive the dysmorphological examination, the incidence of spontaneous abortion; stillbirth; preterm delivery; small-for-gestational age on birth weight, length, head circumference; small for age at 1 year follow-up on weight, length or head circumference.

A pattern of 3 or more minor malformations is defined as any 2 or more infants in the teriflunomide-exposed group who have the same 3 or more specific minor structural defects. Should a pattern exist, comparison would be made to the number of infants, if any, in the comparison group who have the same pattern of 3 or more specific minor structural defects.

The primary comparison group for these outcomes is also the MS disease-matched comparison group Cohort II. The secondary comparison group is Cohort III.

8.3 STATISTICAL METHODS

8.3.1 Primary endpoint

The primary endpoint is rate of major structural defects in live born infants. Due to the expected low incidences of major defects, diagnosed within the first year of life, the primary comparison will be carried out using Fisher's exact test between the teriflunomide-exposed group (Cohort I) and the disease- matched comparison group (Cohort II). Although Cohort II is "matched" to Cohort I on the underlying maternal diagnosis of MS, no a priori matching on disease severity is performed at the time of recruitment. Therefore, measures of MS severity will be addressed as confounders in the analyses comparing Cohort I to Cohort II as described below.

Due to the observational nature of the study, it is necessary to adjust for confounders to address baseline differences between the teriflunomide exposed and the comparison groups.

The potential confounders to be evaluated will be those itemized in the analysis variables in Section 8.2 (e.g., maternal age, MS severity). Confounders will be those variables that modify the odds ratio for the outcome by at least 10% in logistic regression with exposure to teriflunomide and the potential confounder as predictors. In addition, any variable that is deemed to be clinically relevant will be considered for inclusion in multivariate analysis even if the 10% criterion is not met. The adjustment for confounders will be carried out using logistic regression, the primary outcome variable as the dependent variable, and with confounders included in the models as independent variables adjusting for the effect of exposure. Stepwise procedures will be used in case of many identified confounders, as sample size permits. Propensity scoring methods will be considered. The analysis of major birth defects will be further stratified based on prenatal diagnosis performed prior to enrollment or not.

Secondary comparisons will be made between the teriflunomide exposed group (Cohort I) and the healthy comparison group (Cohort III). The rate of major structural defects will also be compared to the most recently available rate from the MACDP.

8.3.2 Secondary endpoints

The secondary endpoints of this study include: proportion of major structural defects in all pregnancies excluding lost-to-follow-up, prevalence of a specific pattern of 3 or more minor structural defects in the live born infants who receive the dysmorphological examination, rates of spontaneous abortion, preterm delivery, proportion of live born infants who are small for gestational age (less than or equal to 10th percentile for gestational age and sex) on weight, length or head circumference, and proportion of infants less than or equal to the 10th percentile for sex and age on weight, length or head circumference at 1 year postnatal evaluation. The above endpoints, other than spontaneous abortion and preterm delivery, are binary and will be analyzed in the same fashion as major structural defects, with the exception that the Chi-squared test will be used for comparison between the exposed and the comparison group when the events are not rare. For spontaneous abortion and preterm delivery, survival analyses incorporating left truncation for spontaneous abortion (women may enroll in the study any time between 0 to 20 weeks of gestational age) and right censoring when the subject is no longer at risk of the event are conducted. The comparison between the exposed and the comparison group will be carried out using log-rank test, and confounders will be adjusted using the Cox proportional hazards regression model.

For all endpoints, exposure effect will also be investigated using the timing and dose of exposure, in a fashion similar to using the group indicator as above.

Also influencing fetal exposure is the success of the cholestyramine elimination procedure. Therefore, detailed data on the dose, gestational timing of the elimination procedure (s) and adherence to the guidelines for drug elimination procedure will be incorporated into the analysis of exposure in relation to outcome, and these maternally collected data will be supplemented by medical records and blood levels as available.

8.3.3 Pregnancies resulting in multiple births

For the primary endpoint:

- Major Structural Defects: In pregnancies that result in multiple births where one or more multiples are malformed, the pregnancy will be counted as one malformed outcome.

For secondary end points:

- Patterns of Minor Malformations: In pregnancies that result in multiple births where one or more multiples have 3 or more minor malformations all infants will be considered in establishing a pattern but only 1 infant of a multiple will count towards the minimum of 2 to establish the pattern.

- Spontaneous abortion: if all multiples are aborted, the outcome is considered one spontaneous abortion. If one or more fetuses survive to live birth, the outcome is considered live birth, and the spontaneous loss(es) are footnoted in study periodic tables as it is unknown what proportion of multiples result in singleton live births.

- Preterm delivery and Small for Gestational Age (SGA): Multiples are excluded from these analyses as they are at inherent high risk of these outcomes.

8.4 DETERMINATION OF SAMPLE SIZE

Based on previous experience with the OTIS Autoimmune Diseases in Pregnancy Project, it is estimated that subjects will be an average of 6-9 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 <2%, the estimated lost-to-follow-up rate is 4% (based on previous OTIS experience) resulting in approximately 64 live born infants from a total of 75 enrolled in the teriflunomide-exposed group and 106 live born infants in each comparison group from a total of 125 enrolled in each group at the end of 5 years of recruitment. Experience with the current OTIS Autoimmune Diseases in Pregnancy Project has demonstrated a yield of approximately 90% live born infants from the total proportion enrolled. Therefore, the estimated yield of 85% in this proposal is conservative. We estimate baseline rates of major structural defects, spontaneous abortion, premature delivery, and small for gestational age based on previous OTIS studies and on general population data. With this sample size, at 80% power and 2-sided significance level of 0.05, using Fisher's exact test we will be able to detect a relative risk of 5.57 for proportion of major structural defects in the teriflunomide exposed group versus the diseased matched comparison group, which has an assumed major structural defect rate of 3%, which is the background rate of the external comparison group (MACDP). There is no evidence of an increased risk of major structural defects in general in women with MS. The following table also provides the type of differences that can be detected between the primary comparison groups for a pattern of minor malformation, spontaneous abortion, preterm delivery, and small for gestational age, given the baseline rates assumed in the comparison group, with at

least 80% power and 2-sided significance level of 0.05, under the sample size, except as otherwise noted(13).

The sample size selected and the associated detectable relative risk is due to the relative rarity of expected exposures given the Pregnancy Category X designation and the extensive efforts by health-care providers and women to avoid pregnancy exposures. The sample size and detectable relative risk could only be increased by failure of pregnancy prevention efforts. However, the strength of the proposed approach, despite small sample size, is the high level of scrutiny of exposed pregnancy outcomes with dysmorphological exams (at the same level in controls) in terms of detecting any pattern of malformation and/or any consistency with malformations reported in animal data.

Table 3 - Sample Size and Detectable Effect Size

Outcome	Sample Size Exposed Cohort I: Comparison Cohort II	Baseline Rate in Disease-Matched Comparison Cohort II	RR or % in Exposed*
Major Structural Defects	64:106	3%	5.57
Specific Pattern of 3 or more minor structural defects	64:106	0%	8.5%
Spontaneous Abortion	75:125	10%	2.55
Premature Delivery	64:106	6%	3.50
SGA Small for Gestational Age	64:106	10%	2.68

*Fisher's exact test for major structural defects; one-tailed Fisher's exact test for pattern of minor structural defects; chi-square test for all other outcomes

For the comparison of a specific pattern of 3 or more minor structural defects, the pattern itself must be comprised of at least 2 infants in the exposed group who have the same 3 defects, and this is compared to the incidence of that same pattern in the comparison group; therefore a 1-tailed test is used, and the estimate of the incidence in the comparison group is 0. The sample size is sufficient to detect an incidence rate of 8.5% of a specific pattern in the exposed group (or approximately 5 children) which is comparable to the 10% incidence of a specific pattern of minor structural defects associated with other known human teratogens of moderate risk such as anticonvulsant medications.

9 PHARMACOVIGILANCE

The OTIS Research Center, using the FDA MedWatch form(14), will report to the Sponsor within 1 business day of becoming aware of the event all major structural defects, spontaneous abortions, stillbirths, and neonatal deaths occurring in a teriflunomide-exposed pregnancy. All other endpoints of the study will be included in the summary tables in the periodic annual reports. In addition, women who do not qualify for the study or who decline enrollment will be referred to the Sponsor.

The primary focus of the Teriflunomide Pregnancy Outcome Exposure Registry study is the controlled cohort with specified criteria for inclusion and exclusion and two internally generated comparison groups. However, information gained from teriflunomide-exposed pregnancies that do not qualify for the cohort study can help inform and illuminate findings or conclusions from the cohort study. Therefore, the registry study will also enroll women with teriflunomide exposure anytime during pregnancy, who do not meet inclusion criteria for the cohort study, as an exposure series, and data collection for these pregnancies will be identical

to that outlined in Section 7.2 to the extent possible (see Registry Case Report Management Section 10.3)

9.1 REGULATORY AGENCY REPORTING CONSIDERATIONS

In the United States, the registry study follows the FDA Guidance for Industry for regulatory reporting of SAEs to FDA (Food and Drug Administration, 2002) (5). "The Agency considers pregnancy exposure registry study 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 15 calendar-days".

In Canada, the registry study follows the Health Canada Guidance document for Industry – Reporting Adverse Reactions to Marketed Health Product (in accordance with the Food and Drug Regulations). Health Canada considers registries as solicited reporting. Therefore, in Canada, the sponsor is responsible for reporting all serious domestic adverse reactions (AR), serious unexpected foreign AR and reports of domestic unusual failure in efficacy to Marketed Health Products Directorate (MHPD) within the 15-day period specified in the Regulations. For the purpose of AR reporting, solicited reports should only be submitted if there is a reasonable possibility that the health product caused the AR.

For FDA status reporting the registry study Annual Report can be appended to the submission as described in the FDA Guidance. The Annual Report contains the background, study design, and analysis plan. It summarizes the study status and the cumulative data on the registry study to date. In addition, OTIS can generate individual line listings to assist the Sponsor in preparation of their submission. The reports generated and line listings will be current to the most recent data cutoff period.

9.2 SERIOUS ADVERSE EVENTS

For this registry study, the primary outcome of interest is major birth defects occurring in the first year of life in the offspring of a pregnant patient exposed to teriflunomide during pregnancy. Major birth defects, as well as spontaneous abortions, stillbirths and neonatal deaths are considered serious adverse events and will be reported to the sponsor if the event occurred in an enrolled pregnancy with exposure to teriflunomide. Other adverse outcomes that are endpoints of the study, such as preterm delivery and small for gestational age birth size, will be included by Cohort in outcome tables that are prepared for each of the annual Interim and the Final reports, and adverse events are line-listed in these reports. If a woman experiences a non-pregnancy related AE, she will be referred to the Sponsor's Pharmacovigilance call center so that information can be collected and an ICSR created. To expedite this process, if possible, the woman will be transferred to the Pharmocovigilance call center while she is on the Study center call line.

9.3 REPORTING OF SERIOUS ADVERSE EVENTS

The OTIS Coordinating Center reports within 1 business day of becoming aware of the event to the sponsor's safety department all major birth defects, spontaneous abortions, stillbirths, and neonatal deaths following teriflunomide exposure in pregnancy, regardless of whether the event is expected or unexpected, or attributed to teriflunomide. OTIS will provide this information to the sponsor using the MedWatch format. The sponsor will report SAEs to regulatory authorities in accordance with 21 Code of Federal Regulations (CFR) 314.80, FDA Guidance to Industry, Establishing Pregnancy Registries (2002)(5) and Canadian Food and Drug Regulations.

10 MANAGEMENT OF DATA

10.1 DATA 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 Autoimmune Diseases in Pregnancy Project.

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 bi-monthly basis, and 100% of key variables are double-checked for data entry accuracy. The study statistician will also conduct quarterly 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.

10.2 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 performed on a monthly basis is provided by blinded review of co-investigator, Dr. Kenneth Lyons Jones.

10.3 MANAGEMENT OF REGISTRY CASE REPORTS

The focus of the study will be the hypothesis-driven cohort study; however, the registry study will also function as a repository for case reports of teriflunomide-exposed pregnancies and outcomes that do not qualify for the cohort study. In other words, teriflunomide-exposed pregnancies that do not qualify as eligible for the cohort study will be consented into the case report series. The management of these types of reports and how they will be analyzed is outlined in this section. These include retrospectively reported cases, first contact with the Study Research Center after 20 completed weeks' gestation, exposure to teriflunomide only after 12 weeks from LMP, first contact with the Study Center after prenatal diagnosis of a major structural defect, women enrolled with a previous pregnancy, and any off-label uses of teriflunomide. Women whose pregnancies fall into 1 or more of these categories, and who agree to participate in the study will be consented and data collected as described for the cohort study to the extent possible, as outlined in Section 7.3, including the dysmorphological examination of live born infants and release of medical records.

10.3.1 Sources of registry case reports

Case reports that do not qualify for the prospective cohort study may come to OTIS from health care providers, pregnant women, or be referred by the sponsor's safety or pharmacovigilance group.

10.3.2 Woman initiated registry case reports

Women who contact the OTIS registry study staff and who do not meet the criteria for the prospective study, for example, women who have already had prenatal diagnosis of a fetus with a major congenital defect or who contact the OTIS registry study staff after 20 completed weeks' gestation following a first trimester teriflunomide exposure, or who contact the OTIS registry study staff retrospectively will be consented, interviewed, medical records requested, and the dysmorphological outcome examination will be performed using the same protocol as prospectively enrolled participants in the cohort and outlined in Section 7.3. However, these participants will not be included in the primary analysis for the cohort 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).

10.3.3 Health care provider initiated Registry case reports

If the OTIS registry study staff is initially contacted by the HCP, he or she will be asked to have the pregnant patient contact the OTIS registry study staff to provide informed consent. If the patient declines contact with the OTIS registry study staff, the HCP and/or the mother will be encouraged to report directly to the sponsor.

10.3.4 Sponsor safety surveillance or pharmacovigilance/PMP (Patient Management Program)

The sponsor will encourage pregnant women and HCP's who contact the sponsor following exposure to contact the OTIS registry study staff directly. Those who qualify for and enroll in the cohort study will be included. Those who do not will be asked to enroll in the registry study as a case report.

10.3.5 Reports from published literature

In addition to data collected from registry study participants, a systematic search of the literature will be conducted in advance of each interim and final registry study report to identify relevant publications, and these will be included as appendices to the periodic and final registry study reports prepared by OTIS.

10.3.6 Information from other studies

As other data sources on pregnancy outcomes following maternal exposure to teriflunomide during pregnancy become available (e.g., clinical trials), they may be summarized and included in the appendices of the registry study periodic and final reports.

10.4 MONITORING METHODS FOR REGISTRY CASE REPORTS

The intent of the registry study is to determine whether there is a signal that might indicate a potential risk of major birth defects in the offspring of pregnant women following an exposure to teriflunomide during pregnancy. The major strength of the registry study is that the data is collected in the prospective cohort study, before there is a known outcome of the pregnancy. For this reason there is no potential for bias in ascertainment based on known outcome. In addition, the prospective cohort study involves comparison to 2 control groups (disease-matched and healthy) that are internally and contemporaneously generated and provide more appropriate comparisons than general population statistics. Furthermore, the prospective study includes a level of outcome evaluation with a dysmorphological examination that exceeds that of any other method.

Registry study case reports, outside the cohort, can be used to illuminate knowledge gained from the cohort study, for example, to determine if an unusual pattern of malformation identified in the cohort study is or is not also noted in any infants in the case report series. Therefore, the OTIS Scientific Advisory Committee and the investigators will consider the

Registry study case reports when reviewing the cohort study data for the appearance of any unusual events, problem cases, or unexpected numbers of specific events. All reports of major birth defects are transmitted promptly to the sponsor to meet regulatory reporting.

10.5 STATISTICAL CONSIDERATION FOR REGISTRY CASE REPORTS

The primary population for analysis will be those enrolled in the prospective cohort study and this plan for analysis has been presented in previous sections.

Only descriptive statistics will be presented for Registry study case reports not included in the prospective cohort, as there is no known denominator of exposed women for such reports, no comparison group, and these reports inherently involve potential bias, particularly if they are retrospective in nature.

11 TASKS AND RESPONSIBILITIES

11.1 RESPONSIBILITIES OF STUDY COMMITTEES

The OTIS Scientific Advisory Committee is composed of experts in the fields of birth defects epidemiology, dysmorphology/medical genetics, and neurology. The Committee will review the aggregated registry data on at least an annual basis in the form of the Interim and Final reports, and may request to review additional information on specific cases. Members of the Committee provide advice to the registry study investigators on interpretation of the data and provide advice on strategies for the dissemination of information regarding the registry study. An annual report is prepared in advance of each meeting to summarize these aggregate data, is shared with the sponsor, and is finalized with the Committee's comments and recommendations.

The Advisory Committee is chaired by a designated member of the Committee. The Committee will meet at least annually.

11.2 RESPONSIBILITIES OF THE INVESTIGATOR

The investigators will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

The OTIS Research Center, wherein the registry study will reside, is responsible for maintaining current Institutional Review Board (IRB) approval at the University of California San Diego, for following all IRB regulations, for the collection, management, and follow-up of pregnancy exposures to the registry study, conducting the analysis of the data, updating of the registry study annual reports, and preparation of publications resulting from the registry study. In addition, the OTIS Research Center schedules, plans, and conducts the OTIS Scientific Advisory Committee meetings, and forwards reports of the designated SAEs to the sponsor within 1 business day of becoming aware of the event. The OTIS Research Center is responsible for increasing awareness of the registry study through direct mailings, contacting groups and organizations that 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 OTIS Research Center is also responsible for communicating final results of the study to the study participants.

It is the investigator's responsibility to obtain oral consent from patients, prior to inclusion in the study and followed by written consent, to fill in the Case Report Form (CRF) and to record all data pertinent to the investigation. She/he will ensure that the information reported in the CRF is precise and accurate.

The investigator, or a person designated by the investigator, and under the investigator's responsibility, should fully inform the patient of all pertinent aspects of the study including

the written information. All patients should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the study, the oral Informed Consent Form (ICF) should be filled in and personally dated by the person who conducted the consent conversation. Following oral consent, and before completion of the physical examination, the written ICF should be filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF will be provided to the patient.

11.3 RESPONSIBILITIES OF THE SPONSOR

The sponsor of the study is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

The sponsor is responsible for local health authority submissions and with complying with data protection rules and local requirements.

12 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

12.1 ETHICAL PRINCIPLES

This study will be conducted in accordance with the principles laid by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments.

12.2 LAWS AND REGULATIONS

This study will be conducted in accordance with the guidelines for Good Epidemiology Practice (GEP) International Society for Pharmacoepidemiology, 1996(15); IEA European Federation, 2004)(16). Each participating country should locally ensure all necessary regulatory submissions (e.g., IRB/IEC) are performed in accordance with local regulations including local data protection regulations.

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

This registry study 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 (1996), 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) (U.S. Department of Health and Human Services, 2003).

12.3 DATA PROTECTION

The participant's personal data shall be treated in compliance with all local applicable laws and regulations. When archiving or processing personally identifiable data pertaining to the participants, OTIS Research Center staff shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party(17).

OTIS Research Center staff makes every effort to ensure patient confidentiality within the registry study. When information on reports is distributed to the OTIS Scientific Advisory Committee members, no health care provider information or direct personal identifiers are included. Contact information is not shared outside the OTIS Research Center except with the sponsor for regulatory safety surveillance purposes when reporting major birth defects,

spontaneous abortions, stillbirths, and neonatal deaths, and then only with permission of the participant.

The participant and infant health information in summary form from the limited dataset of protected health information is shared with the sponsor and the OTIS Scientific Advisory Committee, but is not reported in the registry study Annual Report or any other publications or presentations.

12.4 INSURANCE

Participating countries may contract insurance according to local specific requirements.

12.5 SECRECY AGREEMENT

All material, information (oral or written) and unpublished documentation provided to the investigator (or any action carried out by the company on their behalf) by the sponsor (s) are exclusive property of the sponsor(s). These materials or information (both global and partial) cannot be given or disclosed by the investigators or by any person of her/his group to unauthorized persons without the prior formal written consent of the sponsor. The Investigator shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

12.6 RECORD RETENTION

The investigator shall arrange for the retention of study documentation for a minimum of 10 years after the end of the study. In addition the investigator will comply with specific local regulations/ recommendations with regards to participant record retention.

12.7 PREMATURE DISCONTINUATION OF THE STUDY

The sponsor can decide at any time and for any reason to prematurely stop or to interrupt the study including discontinuation of the manufacture of teriflunomide; the decision will be communicated in writing to the investigator. Similarly, should the investigator decide to withdraw from the study, she/he will immediately inform the Sponsor in writing. If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC) and Competent Authorities should be informed.

Discontinuation of the registry study will be considered at such time as:

- Sufficient information has accumulated to meet the scientific objectives of the registry study,
- 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 OTIS investigator and the sponsor will notify the IRB and Health Authorities of study discontinuation/termination. These considerations are documented in the FDA Guidance document.

12.8 SPONSOR AUDITS AND INSPECTIONS BY COMPETENT AUTHORITIES

The investigator agrees to allow sponsor auditors/competent authority's inspectors to have direct access to his/her study records for review with the understanding that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The investigator will make every effort to help with the performance of the audits and inspections giving access to all necessary facilities, data, and documents.

As soon as the investigator is notified of a future inspection by the authorities, he/she will inform the sponsor and authorize the sponsor to participate in this inspection. The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the competent authorities will be immediately communicated by the investigator to the sponsor.

The investigator shall take appropriate measures required by the sponsor to take corrective actions for all problems found during the audit or inspections.

13 PROTOCOL AMENDMENTS

Any change to the protocol will be recorded in a written amendment, which will be signed by the investigator and by the sponsor and the signed amendment will be attached to this protocol. Amendment to the protocol may require regulatory submissions (e.g., IRB/IEC) in accordance with local regulations. In some cases, an amendment may require a change to the ICF.

14 DOCUMENTATION AND USE OF THE STUDY RESULTS

14.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

Unless otherwise specified by local laws and regulations, the study investigators and the University of California San Diego retain ownership of data and rights to publication of results and findings related to this study. The sponsor reserves the right to use data from the periodic and final reports generated from this study for any purpose including submitting them to the Competent Authorities of any country.

The OTIS Scientific Advisory Committee will have full access to the periodic summary reports and the final study report. The registry study investigators, data collection and management staff reside at the OTIS Autoimmune Diseases in Pregnancy Project in the OTIS Research Center located at the University of California, San Diego. These personnel, under the supervision of the investigators, have access to the physical files and electronic data. Sponsor representatives through the OTIS Scientific Advisory Committee have access to summary data in aggregate as part of the annual periodic and final review. The OTIS Scientific Advisory Committee will receive information on individual events as part of the annual report. Contact information is not included in any listings provided. The Scientific 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.

14.1.1 Participant 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 OTIS Research 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.

14.1.2 Published data

Care is taken to assure that a participant is not identifiable in the data tables published in the interim reports, or other publications. No protected health information is included in any published information. Ad hoc requests for registry study information are reviewed and approved by the OTIS investigators with the advice of the Scientific Advisory Committee.

14.2 PUBLICATIONS

It is the policy of the sponsor to encourage the presentation and/or publication of the results of its studies using validated data so that the accuracy of the results can be ensured.

The registry study investigators and the OTIS Research Group are responsible for presentations and/or publications resulting from the Registry study.

The final decision to publish any manuscript/abstract/presentation will be made by the investigators after prior notice to the sponsor allowing for its internal review and comments. All manuscripts must be submitted to the internal review of the sponsor at least 45 calendar days in advance of submission. The sponsor may request that the sponsor's name and/or names of 1 or several of its employees appear or do not appear in such publication.

The sponsor can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein, as specified in the study contract.

The OTIS registry study staff will initiate presentations at scientific and professional meetings, and will publish descriptive progress as appropriate in abstract form at interim points and final results at the completion of the registry study. The OTIS registry study staff will use these and several other strategies to raise awareness of the registry study. However, the OTIS registry study staff never identifies individual subjects or share their list of providers.

14.2.1 Annual reports

Annual reports will be issued to the sponsor and the OTIS Scientific Advisory Committee in conjunction with the annual OTIS Scientific 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 OTIS registry study, and provide descriptive analysis of prospectively reported pregnancy outcomes in this registry study.

14.2.2 External requests for use of the data

The OTIS Advisory Committee drafts policy for managing external requests for data analysis or use of information from the annual reports. Data analyses to support these activities are conducted by the OTIS registry staff.

15 REFERENCES

1. Tsui A & Lee MA. Multiple sclerosis and pregnancy. Curr Opiin Obstet Gynecol 2011 23:435-9.

2. Nelson JL & Ostensen M. Pregnancy and multiple sclerosis. Rheum Dis Clin North Am 1997;23(1):195-212.

3. Jalkanen A, et al. Pregnancy outcome in women with multiple sclerosis: results from a prospective nationwide study in Finland. Multiple Sclerosis 2010: 16:950-55.

4. Honein MA, Paulozzi LJ, Cragan JD, Correa A. Evaluation of selected characteristics of pregnancy drug registries. Teratology 1999;60:356-64.

5. Food and Drug Administration. Guidance for industry: Establishing pregnancy exposure registries. Rockville (MD): US Department of Health and Human Services, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research; 2002. Available from URL: http://www.fda.gov/cber/gdlns/pregnancy.pdf.

6. Henshaw SK. Unintended pregnancy in the United States. Fam Plann Perspect 1998 Jan-Feb;30(1):24-9, 46.

7. Finer LB & Zolna MR. Unintended pregnancy in the United States: incidence and disparities. Contraception; 2011:84:478-85.

8. Chambers CD, Braddock SR, Briggs GG, et al. Postmarketing surveillance for human teratogenicity: a model approach. Teratology 2001;64:252-61.

9. Centers for Disease Control and Prevention. Metropolitan Atlanta Congenital Defects Program. Surveillance procedure manual and guide to computerized anomaly record. Atlanta (GA): US Department of Health and Human Services, Public Health Service; 1998.

10. Chambers CD, et al. Birth outcomes in women who have taken leflunomide in pregnancy. Arthritis and Rheumatism; 2010: 62:494-503.

11. Leen-Mitchell M, Martinez L, Gallegos S, Robertson J, Carey JC. Mini-review: history of organized teratology information services in North America. Teratology 2000;61:314-7.

12. Centers for Disease Control and Prevention. Update on overall prevalence of major birth defects – Atlanta, Georgia 1978-2005. MMWR Morb Mortal Wkly Rep 2008;57:1-5

13. Xu R & Chambers C. A sample size calculation for spontaneous abortion in observational studies. Reproductive Toxicology, 2011; 32: 490-493.

14. FDA MedWatch: MedWatch: The FDA Medical Products Reporting & Safety Information Program (5600 Fishers Lane, Rockville, MD 20852-9797, 800 FDA 0178). Available from URL: http://www.fda.gov/medwatch/

15. International Society for Pharmacoepidemiology. Guidelines for good epidemiology practices for drug, device, and vaccine research in the United States. March 27, 1996. Available from URL: http://www.pharmacoepi.org/resources/goodprac.htm.

16. IEA European Federation, 2004. 'Good Epidemiological Practice (GEP) proper conduct in epidemiology research'.

17. US Department of Health and Human Services. Protecting personal health information in research: Understanding the HIPAA rule. National Institutes of Health (NIH) Publication Number 03.5388 2003. Available from URL: http://privacyruleandresearch.nih.gov.