NOVARTIS

MotherToBaby PREGNANCY STUDIES

Chief Medical Office & Patient Safety

Non-Interventional Study Protocol (PASS)

REDACTED PROTOCOL

BAF312A2403

Title	**Post-Authorization Safety Study for Assessment of Pregnancy Outcomes in Patients Treated with Mayzent (siponimod): An OTIS Observational Pregnancy Surveillance Study**
Protocol version identifier	v1.1 (clean)
Date of last version of protocol	15-November-2022
EU PAS register number	Not applicable
Active substance	Siponimod (ATC code: L04AA42)
Medicinal product	Mayzent, BAF312A
Product reference	Mayzent NDC 0078-0986-15, 0078-0979-12, 0078-0979-50, 0078-0979-92, 0078-0986-93
Procedure number	FDA/PMR 3591-4

Name of marketing authorization holder(s)	Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936-1080, US
Joint PASS	No
Research question and objectives	Research question: "Is exposure to siponimod therapy during pregnancy associated with an increased risk of adverse pregnancy or infant outcomes?" The primary objective is to estimate and compare the prevalence of major structural defects in siponimod exposed pregnant women versus 1) disease-matched pregnant women not exposed to siponimod, and 2) healthy pregnant women. Secondary objectives are to estimate and compare the prevalence of selected adverse pregnancy and infant outcomes in siponimod-exposed pregnant women versus 1) disease-matched pregnant women not exposed to siponimod, and 2) healthy pregnant women. The primary outcome of the study is major structural defects, and the secondary outcomes of the study are a pattern of minor structural defects, spontaneous abortion, stillbirth, elective termination, preterm delivery, preeclampsia/eclampsia, small for gestational age infants, and small for age for postnatal growth to one year of age, developmental performance at approximately one year of age, and serious or opportunistic infections in the first year of life.
Country (-ies) of study	United States and Canada (North America)
Author	[redacted] PhD, MPH Principal Investigator [redacted] Tel: [redacted] Email: [redacted]

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis Pharmaceuticals Corp. One Health Plaza East Hanover, NJ 07936-1080
MAH contact person	[redacted], Pharm.D., [redacted] Novartis Pharmaceuticals Corporation One Health Plaza, East Hanover, NJ 07936-1080, USA [redacted]

Table of contents

List of tables

List of abbreviations

AE	Adverse Event
ASQ	Ages and Stages Questionnaire
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
EC	Ethic Committee
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food & Drug Administration
FPFV	First Patient First Visit
GEE	Generalized Estimating Equations
GMA	Global Medical Affairs
GPP	Good Pharmacoepidemiology Practices
HA	Health Authority
HCP	Health Care Provider
HIPAA	Health Insurance Portability & Accountability Act
HR	Hazard Ratio
ICD-9-CM	The International Classification of Diseases, 9th Revision, Clinical Modification
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IPW	Inverse Probability Weighing
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LMP	Last Menstrual Period
LTFU	Lost-To Follow-Up
LPLV	Last Patient Last Visit
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing Authorization Holder

MI	Multiple Imputation
MICE	Multivariate Imputation by Chained Equations
MS	Multiple Sclerosis
NCHS	National Center for Health Statistics
NI	Non-Interventional
NIS	Non-Interventional Study
NVS	Novartis
OTIS	Organization of Teratology Information Specialists
PASS	Post-Authorization Safety Study
PMS	Post Marketing Surveillance
PS	Propensity Score
RR	Risk Ratio
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMD	Standardized Mean Differences
SOP	Standard Operating Procedure
SPMS	Secondary Progressive Multiple Sclerosis
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
US	United States
WHO	World Health Organization

1 Responsible parties

Table 1-1 Responsible parties

Novartis Medical Director	[redacted] Novartis Pharmaceuticals Corporation One Health Plaza East Hanover, NJ, USA [redacted]
Main protocol author(s) Principal Investigator (PI)	[redacted], PhD, MPH Tel [redacted] Email: [redacted]
Co-investigator (PI)	[redacted], MD
Co-investigator (PI)	[redacted], PhD, MD

2 Abstract

Title

Post-Authorization Safety Study for Assessment of Pregnancy Outcomes in Patients Treated with Mayzent (siponimod): An OTIS Observational Pregnancy Surveillance Study

Version and date

v1.1 15 November 2022

Name and affiliation of main author

[redacted], PhD, MPH
Principal Investigator
[redacted]

Rationale and background

Mayzent (siponimod) is a selective sphingosine 1 - phosphate receptor modulator that causes lymphocyte sequestration in the lymph nodes and presumably reduced migration to the central nervous system (Behrangi et al 2019). Mayzent is approved in the United States (US) for the

treatment of relapsing forms of multiple sclerosis (MS) including clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults and in Canada for the treatment of patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features characteristic of multiple sclerosis inflammatory activity, to delay the progression of physical disability.

Mayzent has been found to have a teratogenic and embryotoxic effect in studies in rats. Furthermore, the receptor family modulated by Mayzent (sphingosine 1‑phosphate receptor) is known to be involved in vascular formation during embryogenesis. Data on Mayzent exposure during pregnancy in the clinical program is very limited and it is not known whether Mayzent can affect pregnancy and infant outcomes in humans. Since it takes approximately 10 days to eliminate Mayzent from the body after stopping treatment, any drug administration on or after the 4th day post the first day of the last menstrual period (LMP) and up to the end of pregnancy may expose the fetus to the drug. This exposure period is derived by taking the conception date (operationalized here as first day of LMP+14 days) as the start of pregnancy and accounting for the above stated Mayzent elimination period (10 days). Based on the pathophysiological considerations and the potential for drug exposure during pregnancy, an evaluation of the effects of drug exposure immediately before and during pregnancy is warranted.

Reference is made to the approval letter for Mayzent dated March 26, 2019 and specifically the post-marketing requirement (PMR) 3591-4. The Mayzent Pregnancy Registry will be conducted to fulfill PMR 3591-4

The Pregnancy Exposure Registry is sponsored by Novartis and conducted by the Organization of Teratology Information Specialists (OTIS) Research Group. It is administered by investigators at the coordinating site located at the [redacted].

This is a United States (US) based registry designed to monitor pregnancy and infant outcomes among women in the US and Canada exposed to siponimod when used in accordance with the current approved prescribing informations in the US and Canada.

The goal of the Registry is to conduct an observational, prospective cohort study that will involve follow-up of live born infants to 1 year of age.

Research question and objectives

Research question: “Is exposure to siponimod therapy during pregnancy associated with an increased risk of adverse pregnancy or infant outcomes?”

To answer this research question, the investigators will monitor pregnancy and infant outcomes in women in the US and Canada exposed to siponimod during pregnancy.

Objective:

The primary objective is to estimate and compare the prevalence of major structural defects in siponimod exposed pregnant women versus 1) disease-matched pregnant women not exposed to siponimod, and 2) healthy pregnant women.

Secondary objectives are to estimate and compare the prevalence of selected adverse pregnancy and infant outcomes in siponimod-exposed pregnant women versus 1) disease-matched pregnant women not exposed to siponimod, and 2) healthy pregnant women.

The primary outcome of the study is major structural defects.

The secondary outcomes of the study are:

- Spontaneous abortion
- Stillbirth
- Elective termination
- Preterm delivery
- Preeclampsia / eclampsia
- Small for gestational age infants
- Small for age for postnatal growth to one year of age
- A pattern of minor structural defects
- Developmental performance at approximately one year of age
- Serious or opportunistic infections in the first year of life.

Study design

This study will utilize a prospective, observational, exposure cohort design to examine pregnancy and infant outcomes in women and infants who are exposed to siponimod during pregnancy to treat MS. The prevalence of each outcome in women exposed to siponimod and their infants will be compared to those observed in two unexposed comparator groups: a disease-matched comparison group of women who have not used siponimod during pregnancy (unexposed disease-matched comparison group), and a comparison group of healthy women who do not have diagnosis of MS, have not had exposure to a known human teratogen, and have not taken siponimod in pregnancy (healthy comparison group). Pregnant women exposed to siponimod who do not meet the prospective cohort criteria will also be followed as part of an exposure series. All participants will be recruited via voluntary participant registration following informed consent by the pregnant woman for her participation. Participants may withdraw from the study at any time.

An interim feasibility assessment will be performed by the Sponsor after three years from Registry initiation to ensure that the study can meet the sample size requirements within a reasonable timeframe to address the scientific question of interest (i.e. within 10 years from registry initiation). This interim assessment will consider data from the Registry and all available data sources such as real-world evidence studies, pharmacovigilance and marketing.

Setting and study population

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

Three cohorts of women will be enrolled prospectively into the cohort study and followed for pregnancy and infant outcomes:

- Siponimod-Exposed Cohort: Pregnant women with MS exposed to siponimod during pregnancy (i.e. on or any time after the 4th day post the first day of LMP prior to conception) (N = 289)
- Disease-Matched Comparison Cohort: Pregnant women with MS not exposed to siponimod during pregnancy (N = 289)
- Healthy Comparison Cohort: Pregnant women who are neither diagnosed with MS nor with any other autoimmune disease, and not exposed to siponimod or any known teratogenic agent during pregnancy (N = 289)

The term "exposed to siponimod" is used here as synonym to "administered siponimod".

Using the multi-product registry concept, this Mayzent-OTIS pregnancy registry (BAF312A2403), will be leveraged for the Kesimpta-OTIS pregnancy registry sub-study (OMB157G2403). Considering the identical population (inclusion/exclusion criteria) and design, the Kesimpta-OTIS sub-study will use the contemporaneous Mayzent-OTIS pregnancy registry comparator cohorts.

The 'Disease-Matched Comparison Cohort' and the 'Healthy Comparison Cohort' will be common between this study and the Kesimpta-OTIS pregnancy registry sub-study (OMB157G2403) study. The first 125 pregnancies in the two comparison groups from the time of the Kesimpta protocol (OMB157G2403) approval will be eligible for inclusion in both studies (i.e., the current study and the Kesimpta-OTIS pregnancy registry sub-study).

Up to an additional 50 women will be enrolled in an exposure series group. This is a group of women with exposure to siponimod during pregnancy, but who do not meet eligibility criteria for the siponimod-exposed cohort group (e.g. retrospective cases would be enrolled in the exposure series group).

Variables

Exposure will be defined as siponimod treatment any time from the first day of the last menstrual period (LMP) prior to conception + 4 days up to and including the end of pregnancy by maternal report and verified by medical record review, with detailed information on the gestational timing, route of administration, dose, and dates of exposure. Outcome variables include major structural birth defects (including interventions for those defects and outcome up to one year of age), spontaneous abortion, stillbirth, elective termination, preterm delivery, minor structural defects, small for gestational age at birth, small for age on postnatal growth at 1 year of age, developmental performance on the Ages and Stages (ASQ) questionnaire for live born infants at 1 year of age, and serious or opportunistic infections in live born infants through the first year of life. Data will be obtained by maternal report, physical examination, and medical record review. Potential confounders or covariates to be collected include maternal age, race/ethnicity, socioeconomic status, body mass index (BMI), pregnancy and health history, lifestyle factors such as tobacco and alcohol use, comorbidities, medication, vaccine and vitamin/mineral exposures, and prenatal tests. Measures of disease severity will be collected for those enrolled in the siponimod-exposed and disease-matched cohorts. Details regarding definitions will be provided in the Statistical Analysis Plan (SAP) to be developed separately.

Data sources

Data will be collected during maternal interviews and via questionnaires, medical record, pregnancy exposure diary, dysmorphology examination data, and the ASQ. Data will be recorded on hard copies of forms or electronically, 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 OTIS Research Center and developed specifically for OTIS studies.

Study size

The prospective cohort study target sample size is 289 pregnant women who have been exposed to siponimod in pregnancy (i.e. on or any time after the 4th day post first day of the LMP prior to conception), for MS, 289 pregnant women diagnosed with MS not exposed to siponimod during pregnancy (primary comparison group/comparison group 1), and 289 healthy women i.e. women who are not diagnosed with MS, or any other autoimmune disease, and without exposure to siponimod, or any known human teratogen during pregnancy (secondary comparison group/comparison group 2).

The current sample size provides 80% power to detect a risk ratio of approximately 3.0 or greater in major structural defects with reference to the baseline prevalence of 2.8% in the Atlanta metropolitan area (CDC 2017).

Up to an additional 50 women will be enrolled in an exposure series group. This is a group of women with exposure to siponimod during pregnancy, but who do not meet eligibility criteria for the siponimod-exposed cohort group (e.g. retrospective cases would be in this group).

Data analysis

The primary population for analysis will be those enrolled in the prospective cohort study comparing siponimod-exposed pregnancies with MS to the disease-matched cohort and the non-diseased cohort. Statistical analyses of those enrolled in the exposure series who do not meet the cohort study criteria will be descriptive only. All relevant exposure, outcome, and covariate data within each study group will be summarized using descriptive statistics annually. Means and standard deviations will be presented for continuous variables and frequencies and percentages will be presented for categorical variables. At the completion of the study, a final analysis with adjusted comparisons between cohort groups will be performed.

Milestones

Planned dates of study milestones:

Start date of data collection: By December 2021

Last date of data collection: May 2032

Interim report submission: Annually beginning in August 2022 through August 2031

Final study report submission: May 2033

3 Amendments and updates

Table 3-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1.1	15 November 2022	Sections 2 and 7.2	Study settings have been amended to note that the comparator cohorts for this study (BAF312A2403) will be shared with the Kesimpta pregnancy registry OTIS sub-study. Accordingly, the inclusion and exclusion criteria for the comparator cohorts are amended to harmonize between both, Mayzent and Kesimpta – OTIS prengnacy registries.	Since the population under study (i.e. inclusion/exclusion criteria) are the same between this study (BAF312A2403) and the Kesimpta-OTIS pregnancy registry sub-study (OMB157G2403) and the two studies will run in parallel using the same design, the comparator cohorts will be common between both studies. The first 125 eligible pregnancies in the two comparator cohorts from the time of Kesimpta protocol approval will be included in both studies.

4 Milestones

Table 4-1 Planned dates of study milestones

Milestone	Planned date
Start of data collection	By December 2021
End of data collection	May 2032
Interim reports	Annual submission beginning August 2022 through August 2031
Final study report submission	May 2033

5 Rationale and background

Siponimod is approved in the United States (US) for the treatment of relapsing forms of multiple sclerosis (MS) including clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults and in Canada for the treatment of patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features characteristic of multiple sclerosis inflammatory activity, to delay the progression of physical disability. Siponimod has also been approved in the European Union for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator. Siponimod binds with high affinity to S1P receptors 1 and 5. Siponimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which siponimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the central nervous system (Mayzent US PI).

There are no adequate data on the developmental risk associated with the use of siponimod in pregnant women. Based on animal data and its mechanism of action, siponimod can cause fetal harm when administered to a pregnant woman. Reproductive and developmental studies in pregnant rats and rabbits have demonstrated siponimod-induced embryotoxicity and fetotoxicity in rats and rabbits and teratogenicity in rats. Increased incidences of post-implantation loss and fetal abnormalities (external, urogenital and skeletal) in rat and of embryo-fetal deaths, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatal exposure to siponimod starting at a dose 2 times the exposure in humans at the highest recommended dose of 2 mg/day. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown (Mayzent US PI). Based on the pathophysiological considerations and the potential for drug exposure during pregnancy, an evaluation of the effects of drug exposure immediately before and during pregnancy is warranted. The Siponimod Pregnancy Registry will be conducted to fulfill the US Food and Drug Administration (FDA) post marketing requirement (PMR 3591-4) for siponimod .

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 and Lee, 2011; Nelson and Ostensen, 1997; Jalkanen et al, 2010). 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.

6 Research question and objectives

The purpose of the Siponimod Pregnancy Exposure Registry is to evaluate the effect of siponimod exposure on rates of pregnancy and infant outcomes in exposed pregnancies compared to unexposed disease-matched and healthy unexposed pregnancies. The lack of human fetal safety data for siponimod makes such a monitoring system an important component of epidemiologic research on the safety of this drug.

The primary objective is to estimate and compare the prevalence of major structural defects in siponimod exposed pregnant women versus 1) disease-matched pregnant women not exposed to siponimod, and 2) healthy pregnant women.

The primary objective will be evaluated among i) pregnancies ending in at least one live birth, and ii) pregnancies ending in at least one live birth, spontaneous abortion, still birth or termination of pregnancy

Secondary objectives are to estimate and compare the prevalence of selected adverse pregnancy and infant outcomes in siponimod-exposed pregnant women versus 1) disease-matched pregnant women not exposed to siponimod, and 2) healthy pregnant women.

Mayzent exposure is defined as exposure to siponimod any time from the 4th days post the first day of LMP prior to conception up to and including the end of pregnancy.

- The primary outcome of the study is major structural defects.
- The secondary outcomes of the study are:
  - Spontaneous abortion/miscarriage
  - Stillbirth
  - Elective termination
  - Preterm delivery
  - Preeclampsia / eclampsia
  - Pattern of 3 or more minor structural defects
  - Small for gestational age
  - Postnatal growth small for age at approximately one year of age
  - Developmental performance at approximately one year of age
  - Serious or opportunistic infections in the first year of life.

7 Research methods

7.1 Study design

This study will utilize a prospective, observational, exposure cohort design to examine pregnancy and infant outcomes in women and infants who are exposed to siponimod during pregnancy to treat MS. The prevalence of outcomes in women exposed to siponimod and their infants will be compared to those observed in two unexposed comparator groups: a disease-matched comparison group of women who have not used siponimod during pregnancy (from the 4th days post the first day of the LMP prior to conception and throughout pregnancy) but have been diagnosed with MS (disease-matched unexposed comparison group), and a comparison group of healthy women who have no diagnosis of MS, have not had exposure to a

known human teratogen, and have not taken siponimod in pregnancy (healthy comparison group). Although the Registry will follow-up on all pregnancies exposed to siponimod (exposure series), the core of the Registry will be a prospective, observational cohort study designed to ascertain and follow up on pregnancy exposures to siponimod that meet the eligibility criteria and to compare these to the above two unexposed comparator groups. All subjects will be recruited via voluntary participant registration following informed consent by the pregnant woman for her participation. Subjects may withdraw from the study at any time.

An interim feasibility assessment will be performed after three years from registry initiation to ensure that the study can meet the sample size requirements within a reasonable timeframe to address the scientific question of interest (i.e. within 10 years from registry initiation). This interim feasibility assessment will consider data from this Registry and all available data sources such as real-world evidence studies, pharmacovigilance and marketing.

7.2 Setting

The Pregnancy Exposure Registry is sponsored by Novartis (referred later as "Sponsor") and conducted by the Organization of Teratology Information Specialists (OTIS) Research Group, a network of university and health department based telephone information centers serving pregnant women and healthcare providers throughout North America (Leen-Mitchell et al, 2000). These services receive spontaneous telephone inquiries from women and healthcare providers about the safety or risk associated with environmental exposures in pregnancy, including medications. Trained Teratogen Information Specialists at each site provide appropriate risk assessment and referral for all patient and healthcare provider callers free of charge. These services also provide a basis for collaborative research such as this Registry. Thus, individual Teratogen Information Services located throughout the US and Canada will serve as a source of referrals not only for siponimod-exposed pregnancies but also for similarly ascertained disease-matched comparison pregnant women who have not used siponimod in pregnancy and similarly-ascertained healthy pregnant women who have no diagnosis of the approved indication, have not had exposure to a known human teratogen, and have not taken siponimod in pregnancy.

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

The study population includes pregnant women who reside in the US or Canada with siponimod-exposure for the approved indication, and 2 comparison groups without siponimod exposure during pregnancy (1 disease-matched unexposed comparison group, and 1 healthy unexposed comparison group). Since the population under study (i.e. inclusion/exclusion criteria) are the same between this study (BAF312A2403) and the Kesimpta-OTIS pregnancy

registry sub-study (OMB157G2403) and the two studies will run in parallel using the same design, the comparator cohorts will be common between both studies. The first 125 pregnancies in the two comparison groups from the time of Kesimpta protocol (OMB157G2403) approval will be eligible for inclusion in both studies (i.e., the current study and the Kesimpta-OTIS pregnancy registry sub-study).

Based on use of multiple methods for identification and recruitment of exposed women, and the previous recruitment experience of the existing OTIS studies, the investigators have projected that approximately 17-18 pregnant women with exposure to siponimod could be enrolled in the Registry each year, although the true number of exposed pregnancies potentially available for enrollment in the Registry cannot be known at this time.

7.2.1 Study period

The study is planned for about 10.5 years from the enrollment of the first patient in (FPI) until study completion. There will be 7 years of active recruitment, with an annual interim report reviewed by the Scientific Advisory Board each year. The final report with statistical analysis according to the statistical analysis plan (SAP) will be prepared at the end of the study.

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

7.2.2 Eligibility criteria

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

- Residence in the U.S. or Canada at the time of enrollment
- Currently pregnant women
- Verbal consent to participate in the study

7.2.2.1 Inclusion criteria for core prospective study

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

Cohort 1: Siponimod-Exposed Cohort

1. Pregnant women
2. Diagnosed with MS, with the indication validated by medical records when possible
3. Exposure to siponimod for the treatment of MS, for any number of days, at any dose, and at any time from the 4th day post the first day of LMP prior to conception up to and including the end of pregnancy
4. Agree to the conditions and requirements of the study including the interview schedule, release of medical records, the dysmorphology examination of live born infants, and the Ages and Stages Questionnaire (ASQ) in live born children

Cohort 2: Disease-Matched Comparison Cohort (Comparison Group 1)

1. Pregnant women

2. Diagnosed with MS, with the indication validated by medical records when possible
3. May or may not have taken another medication for MS in the current pregnancy (see exclusionary medications Section 7.2.2.2)
4. Agree to the conditions and requirements of the study including the interview schedule, release of medical records, the dysmorphology examination of live born infants, and the ASQ in live born children

Cohort 3: Healthy Comparison Cohort (Comparison Group 2):

1. Pregnant women
2. Agree to the conditions and requirements of the study including the interview schedule, release of medical records, the dysmorphology examination of live born infants, and the ASQ in live born children

7.2.2.2 Exclusion criteria for the core prospective study

Women meeting any of the following criteria will be excluded from the cohort study:

Cohort 1: Siponimod-Exposed Cohort

1. Women who have enrolled in the siponimod cohort study with a previous pregnancy
2. Women who have used siponimod for an indication other than a currently approved indication
3. Women with exposure to any of the following medications within 5 half-lives prior to conception:
   - Cladribine (Mavenclad)
     - Based on the US label, animal studies indicate that there is positive evidence of teratogenicity for Cladribine
   - All other S1P modulators including fingolimod (Gilenya), ozanimod, etc.
     - S1P modulatros are in the same class of drug as siponimod
   - Teriflunomide (Aubagio)
     - The teratogenicity of teriflunomide is unknown and currently under investigation
   - Other anti-CD20 monoclonal antibody: same class as Kesimpta
   - New medications (marketed after 2020) indicated for the treatment of MS will be evaluated for inclusion/exclusion criteria as the study progresses.
4. Retrospective enrollment after the outcome of pregnancy is known (i.e. the pregnancy has ended prior to enrollment)
5. Results of a diagnostic test are positive for a major structural defect prior to enrollment (Section 7.7.2.3). However, women who have had any normal or abnormal prenatal screening or diagnostic test prior to enrollment are eligible as long as the test result does not indicate a major structural defect.

Cohort 2: Disease-Matched Comparison Cohort (Comparison Group 1):

1. Exposure to siponimod any time from the 4th day post the first day of LMP prior to conception up to and including end of pregnancy
2. Women with exposure to any of the following medications within 5 half-lives of conception:
   - Cladribine (Mavenclad)
   - S1P modulators
   - Teriflunomide (Aubagio)
   - Anti CD-20 monoclonal antibody

   New medications (marketed after 2020) indicated for the treatment of MS will be evaluated for inclusion/exclusion criteria as the study progresses.
3. Women who have enrolled in the siponimod cohort or OMB157G2403 Kesimpta cohort with a previous pregnancy
4. Retrospective enrollment after the outcome of pregnancy is known (i.e. the pregnancy has ended prior to enrollment)
5. Results of a diagnostic test are positive for a major structural defect prior to enrollment. However, women who have had any normal or abnormal prenatal screening or diagnostic test prior to enrollment are eligible as long as the test result does not indicate a major structural defect.

Cohort 3: Healthy Comparison Cohort (Comparison Group 2):

1. Exposure to Kesimpta 166 days before or to siponimod any time from the 4th day post first day of LMP prior to conception up to and including end of pregnancy
2. Women who have a diagnosis of a MS or a siponimod approved indication
3. Women who have a current diagnosis of any autoimmune disease
4. Women who have first contact with the project after prenatal diagnosis of any major structural defect
5. Women who have enrolled in the siponimod cohort or Kesimpta cohort study with a previous pregnancy
6. Women treated with Mayzent or Kesimpta for non-MS indication
7. Retrospective enrollment after the outcome of pregnancy is known (i.e. the pregnancy has ended prior to enrollment)
8. Results of a diagnostic test are positive for a major structural defect prior to enrollment. However, women who have had any normal or abnormal prenatal screening or diagnostic test prior to enrollment are eligible as long as the test result does not indicate a major structural defect.
9. Women exposed to a known human teratogen during pregnancy as confirmed by the OTIS Research Center

7.2.2.3 Siponimod-exposed pregnancies not eligible for the siponimod-exposed prospective cohort

By study design, pregnancies that do not meet the exposed cohort criteria for reasons described in Section 7.2.2.2 will be excluded from the cohort analysis; however, information on birth outcomes can be obtained and can be useful when reviewing the cohort data for any evidence of increased risks for the study outcomes. For this reason, women who do not meet the exposed cohort criteria will be invited to enroll in a separate exposure series. Women who are eligible for enrollment in the exposure series include the following: use of siponimod in pregnancy for an unapproved indication and retrospective reports of a siponimod-exposed pregnancy after the outcome of pregnancy is known. With informed consent, data will be collected from maternal interviews, medical records, and the dysmorphology examination using the same protocol as the cohort study to the extent possible.

7.2.2.4 Analysis populations

The Registry will collect and follow-up on reports of all types (i.e., retrospective, exposure after first trimester only, off-label indication, etc.: see Section 7.2.2.3) involving pregnancy exposure to siponimod; however, the core of the Registry will be a prospective cohort study designed to ascertain and follow-up on pregnancy exposures to siponimod and to compare these outcomes to 2 internally-generated comparison groups and one external comparison group (Metropolitan Atlanta Congenital Defects Program, or MACDP).

- Comparison Group 1 consisting of diseased-matched pregnant women who have not been exposed to siponimod at any time from the 4th day post first day of LMP prior to conception up to and including the end of current pregnancy. This will be the primary comparison group.

- Note that this cohort will be common between this study and the Kesimpta-OTIS pregnancy registry sub-study (OMB157G2403). The first 125 eligible pregnancies after OMB157G2403 protocol approval will be eligible for inclusion in both studies.

- Comparison Group 2 consisting of pregnant women who contact the study directly or who are referred to the study, and who do not have MS, have not been exposed to a known human teratogen, and have not taken siponimod in pregnancy. This will be a secondary comparison group.

- Note that this cohort will be common between this study and the Kesimpta-OTIS pregnancy registry sub-study (OMB157G2403). The first 125 eligible pregnancies after OMB157G2403 protocol approval will be eligible for inclusion in both studies.

Based on previous OTIS experience, it is estimated that Comparison Group 2 will be similar to the exposed and primary comparison group on key demographics such as maternal age, socioeconomic status and race/ethnic distribution. However, differences between the cohorts for these demographic factors will be monitored in the annual interim reports and, should they occur, will be addressed in future recruitment efforts and in the statistical analysis phase of the study through methods such as adjustment (to be detailed in the SAP).

7.2.2.5 Modalities of recruitment

All exposed subjects and comparison subjects will be recruited through spontaneous calls to participating OTIS member services in locations throughout North America and through active recruitment strategies, e.g., direct mailings to relevant specialists, obstetric healthcare providers, pharmacists, website, and professional meetings. Each OTIS service will provide exposure counseling in the routine manner for all exposed and unexposed women who initially make contact with the service with questions regarding a current pregnancy. Subsequently, each OTIS service will request permission to refer to the Research Center at the [redacted]. Potential subjects who agree to be referred will contact the Research Center or be contacted if they prefer. The OTIS member services will also refer callers to the Research Center whose exposure to siponimod does not appear to qualify for the cohort study (i.e., retrospective reports), as these will be included in the Registry Exposure Case Series. Healthcare providers can also contact the Registry and refer patients; however, in all cases the mother is the individual who provides informed consent for participation and completes the interview based data collection.

The US and Canada's siponimod package insert contains information about the siponimod pregnancy exposure registry, and encourages healthcare providers to register patients and pregnant women to register themselves by calling the study toll-free number as soon as the pregnancy is known.

In addition, members of the Scientific Advisory Board (see Section 11.3.1) will be asked to promote recruitment among colleagues. The existing Toll Free number for North American callers currently being utilized by all MotherToBaby Pregnancy Studies and the OTIS Autoimmune Diseases in Pregnancy Project [redacted] will be maintained as a considerable amount of previous publicity for this number will enhance ease of contact for patients to the Registry.

The existing MotherToBaby/OTIS Autoimmune Diseases in Pregnancy Project contact and referral information is available on the website and multiple methods are used to increase awareness through the website (https://mothertobaby.org/pregnancy-studies/), social media and print advertising. The FDA website (http://www.fda.gov/womens/registries/default.htm) lists the MotherToBaby/OTIS Pregnancy Studies and will have this Registry added to their listing. The study will also be listed on ClinicalTrials.gov.

This information will also be made available 1) in the prescribing information (package insert) for siponimod and other product literature and promotional materials, and 2) via a link from the Novartis website. Additional venues for publicizing the Registry include: 1) linking the Registry website to other specialty provider and maternal health interest websites, 2) posting notices in appropriate journals or patient advocacy publications, and 3) later, presenting Registry data at specialty provider, and obstetrics-related scientific and clinical meetings. In addition, the Registry will enlist the aid of the U.S. FDA, the U.S. Centers for Disease Control and Prevention (CDC), and other relevant organizations in facilitating patient recruitment, and the Sponsor will also provide information about the Registry at appropriate professional meetings. Additional venues for publicizing the Registry include advocacy groups and patient support networks. The Sponsor may facilitate awareness among prescribers through Medical Science Liaisons.

The Sponsor will encourage exposed women or their Healthcare Providers to contact the Registry directly.

7.3 Variables

Key exposure, outcome and potential confounding variables are defined below in Table 7-1. Additional details regarding definitions will be provided in the SAP to be developed separately, and will provide greater detail on the definitions of, the identification of and the controlling for confounders and/or effect modifiers.

Data will be collected through maternal interview(s) and questionnaires, medical records, a pregnancy exposure diary, a dysmorphology examination of live born infants, and the ASQ for live born infants. Maternal interview(s) include questions about pregnancy history, history of onset and other characteristics of MS, and current medication use. Other variables such as socio-demographics, gestational age, co-morbidities, concomitant medications, disease severity and duration, and other relevant potential confounders will be collected. Exposure and severity data will be collected at enrollment, at 20-22 weeks' gestation, 32-34 weeks' gestation, and 0-6 weeks after scheduled expected date of delivery or earlier if outcome has occurred prior to one of the previous interviews. For live births, infant data are collected at pregnancy outcome, and at approximately 12 months of age. Medical records will be requested from the participant's obstetrician as well as the healthcare provider treating her MS. Medical records are also obtained from the delivery hospital, and the child's pediatrician after birth and at 1 year of age.

Participants are asked to keep track of their pregnancy exposures and pregnancy related tests by filling out a pregnancy exposure diary throughout their pregnancy.

Live born infants are eligible for the dysmorphology examination which is performed by a study physician sometime in the infant's first year of life.

Mothers of live born infants are asked to complete the Ages and Stages developmental screening questionnaire at approximately one year of age.

Table 7-1 Variables

Variable	Role	Data source(s)	Operational Definition
Exposure to siponimod	Exposure	Maternal report Medical record	Maternal report of exposure to siponimod of at least one dose any time from 4th days post first day of LMP prior to conception up to and including the end of pregnancy. Confirmation of exposure with medical records.
Dose of siponimod	Exposure	Maternal report Medical record	Dose of siponimod mg per day (maternal report and confirmation with medical records).

Variable	Role	Data source(s)	Operational Definition
Duration of siponimod use	Exposure	Maternal report Medical record	Weeks of siponimod use in pregnancy (maternal report and confirmation with medical records).
Indication	Exposure	Maternal report Medical record	Indication for use of siponimod (maternal report and confirmation with medical records).
Gestational age at time of initial exposure to siponimod	Exposure	Maternal report Medical record	Gestational age at the time of initial exposure to siponimod (maternal report and confirmation with medical records).
Major structural birth defect	Outcome – primary	Maternal report Medical record OTIS investigator review Dysmorphology Evaluation	The Registry adopts the term “major structural defect” (i.e., birth defect) for an abnormality usually referred to as a “congenital abnormality” and defines major structural defect as follows: Any major structural or chromosomal defect defined and classified, using the CDC Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects (CDC 2017).(including any intervention to correct the structural defect and its outcome) in any pregnancy including those ending in a live born infant or a pregnancy loss.
Minor structural defect	Outcome - secondary	Dysmorphology Evaluation	A defect which occurs infrequently in the population but which has neither cosmetic nor functional significance to the child and is identified using a study related checklist incorporated into the study dysmorphology examination of live born infants.
Spontaneous abortion	Outcome - secondary	Maternal report Medical record	Non-deliberate embryonic or fetal death that occurs prior to 20.0 weeks’ gestation.

Variable	Role	Data source(s)	Operational Definition
Stillbirth	Outcome - secondary	Maternal report Medical record	A non-deliberate fetal death that occurs at or after 20.0 weeks' gestation but prior to delivery.
Elective termination / abortion	Outcome – secondary	Maternal report Medical record	A deliberate discontinuation of pregnancy through medication or surgical procedures.
Premature delivery	Outcome - secondary	Maternal report Medical record	A spontaneous or induced delivery at <37.0 gestational weeks (as counted from LMP), reported by the mother and validated through the medical record.
Preeclampsia / Eclampsia	Outcome - secondary	Maternal report Medical record	Reported by maternal interview and confirmed with medical records.
Small for gestational age	Outcome - secondary	Maternal report Medical record	Birth size (weight, length or head circumference) ≤10th percentile for sex and gestational age using National Center for Health Statistics (CDC, 2000) pediatric growth curves for full term infants. Prenatal growth curves specific to preterm infants will be used for premature infants (Olsen, 2010).
Postnatal growth deficiency	Outcome - secondary	Medical record	Postnatal size (weight, length or head circumference) ≤10th percentile for sex and age using NCHS pediatric growth curves (CDC, 2000), and adjusted postnatal age for premature infants.
Screening for Developmental Milestones	Outcome - secondary	Neurodevelop-mental questionnaires	Screening for neurodevelopment performed using the Ages and Stages Questionnaire (ASQ). An abnormal score is defined in the scoring guidelines.
Serious or Opportunistic Infections	Outcome - secondary	Maternal report Medical record	Defined as tuberculosis, x-ray proven pneumonia, neonatal sepsis, meningitis, bacteremia, invasive fungal infection, pneumocysitis, septic arthritis, osteomyelitis,

Variable	Role	Data source(s)	Operational Definition
			abcess (deep tissue), and infections requiring hospitalization, identified in live born infants up to one year of age.
Maternal Age (years)	Confounder	Maternal report	Maternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34).
Paternal Age (years)	Confounder	Maternal report	Paternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34).
Maternal Race	Confounder	Maternal report	Maternal (Caucasian/White, Black, Asian/Pacific Islander, Native American, Other).
Maternal Ethnicity	Confounder	Maternal report	Maternal (Hispanic, Non-Hispanic).
Maternal Education	Confounder	Maternal report	Maternal Educational Category (years of completed education <12, 12-15, >15).
Socioeconomic Category	Confounder	Maternal report	Hollingshead Socioeconomic Category based on maternal and paternal occupation and education (1-5).
Maternal Height	Confounder	Maternal report	Maternal height (cm).
Maternal Pre-pregnancy body weight	Confounder	Maternal report Medical record	Maternal pre-pregnancy body weight (kg) (confirm with medical record).
Maternal Pre-pregnancy BMI	Confounder	Maternal report	Maternal pre-pregnancy BMI (<18.5, 18.5-24.9, 25-29.9, >=30).
Number of times pregnant	Confounder	Maternal report Medical record	Number of times ever pregnant (1, 2-3, 4-5, >=6) (confirm with medical record).
Previous live birth or stillbirth deliveries	Confounder	Maternal report Medical record	Number of previous live birth or stillbirth deliveries (0, 1-2, 3-4, >=5) (confirm with medical record).

Variable	Role	Data source(s)	Operational Definition
Previous pregnancies ending in spontaneous abortion	Confounder	Maternal report Medical record	Number of previous pregnancies ending in spontaneous abortion (0, 1, 2, >=3) (confirm with medical record).
Previous pregnancies ending in elective termination	Confounder	Maternal report Medical record	Number of previous pregnancies ending in elective termination (0, 1, 2, >=3) (confirm with medical record).
Gestational age	Confounder	Maternal report Medical record	Weeks of pregnancy at time of enrollment, continuous and categorical (<13, 13-19.9, >=20): gestational age is calculated from the first date of LMP.
Referral source	Confounder	Maternal report	Source options: Sponsor, OTIS service, HCP, Internet, Other.
Geographic area of residence	Confounder	Maternal report	Geographic area of residence (e.g., US, Canada).
Disease Symptom/ Severity measures	Confounder	Maternal report	Disease Symptom/Severity measures (exposed and disease-matched cohorts only).
Prenatal, Multivitamin, or Folic acid	Confounder	Maternal report	Prenatal, Multivitamin or Folic Acid supplement use by timing (began prior to conception, post-conception only, not taken at all).
Alcohol use in pregnancy	Confounder	Maternal report	Yes/No. Dose and frequency are captured.
Tobacco use in pregnancy	Confounder	Maternal report	Yes/No. Dose and frequency are captured.

Variable	Role	Data source(s)	Operational Definition
Prenatal diagnostic tests prior to enrollment	Confounder	Maternal report Medical record	Tests performed prior to enrollment (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis).
Prenatal diagnostic tests anytime during pregnancy	Confounder	Maternal report Medical record	Tests performed anytime in pregnancy (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis).
Maternal pregnancy exposure to a known human teratogen	Confounder	Maternal report Medical record	Maternal pregnancy exposure to a known human teratogen (e.g., Type I diabetes) (confirm with medical record).
Years since diagnosis of approved indicated disease	Confounder	Maternal report Medical record	Years since diagnosis of approved indicated disease.
Comorbid maternal medical history	Confounder	Maternal report Medical record	Comorbid maternal medical history (e.g. chronic hypertension, asthma)
Treatment history for the indicated disease	Confounder	Maternal report Medical record	Treatment history for the indicated disease
Pregnancy complications	Covariate	Maternal report Medical record	Pregnancy complications, including infection and gestational diabetes.

7.4 Data sources

Data will be collected using maternal interview(s), medical record review, pregnancy exposure diary, physical examination data, and neurodevelopmental questionnaire data (ASQ). Data will be recorded on hard copies of forms and these records will be retained by OTIS at the OTIS Research Center. These forms are considered the primary data sources for the study. Data from

these forms will be extracted and entered into a customized OTIS study database located in the Research Center and developed specifically for the OTIS studies. In addition, the Expanded Disability Status Scale (EDSS) (Koblet et al, 2006) assessing disease severity/activity will be administered to participants with MS, and collected from medical records when available.

Medications or vaccine exposures entered into the database will be coded using the Slone Drug Dictionary. Major malformations will be coding using the MACDP coding list. This coding system will be used in all annual interim and final reports, as well as the final analysis.

Safety data will be transferred to Novartis at a frequency as defined in Section 9 of this protocol. An interim report will be provided annually to the Sponsor containing descriptive data only on characteristics of women enrolled in the study and cumulative study outcomes. No statistical comparisons are planned for the annual interim reports. The final report and statistical analysis report will be provided to the Sponsor after closure of the study.

7.4.1 Data collected

Data on the number of pregnant women referred into the study, number eligible for enrollment, number consented, unable to contact, or declined participation will be collected and summarized monthly by the OTIS Research Center.

7.4.2 Disposition of patients

Women who are not eligible for enrollment in the study or who decline are tallied in monthly and cumulative recruitment reports, but these data are not included in the annual interim or final study reports.

7.4.3 Participant data

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

7.4.3.1 Intake/Enrollment interview

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

7.4.3.2 Interim interview I and II (~20 and 32 weeks' gestation)

Following the initial intake interview, participants will be sent a pregnancy exposure diary on which they will be asked to record any additional exposures (medications, vaccinations, vitamins, etc.) or events as the pregnancy progresses. Along with the pregnancy exposure diary, each woman will be sent a copy of the written informed consent document, and a research HIPAA compliant obstetric medical record release form.

Women who have enrolled in the study prior to 18 weeks post-LMP will be interviewed by telephone at 20-22 weeks post-LMP, 32-34 weeks post-LMP and within 0-6 weeks after the expected due date. Women who have enrolled between 18 and 20 weeks post-LMP will be interviewed at 32-34 weeks post-LMP and within 0-6 weeks after the expected due date.

Women who enrolled after 20 weeks post LMP and before 30 weeks post-LMP will be interviewed at 32-34 weeks post-LMP and within 0-6 weeks after the expected due date. Women who have enrolled after 30 weeks post-LMP will be interviewed within 0-6 weeks after the expected due date (See Table 7-2).

The purpose of these interviews will be to update records of pregnancy exposures and results of prenatal tests, to remind women to maintain the pregnancy exposure diary, to update phone number and address information, and to determine if the pregnancy has ended prior to the expected due date.

7.4.3.3 Pregnancy outcome interview

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

The outcome interview for live born infants will be a structured telephone interview and information will be elicited on the following: date of delivery, hospital location and mode of delivery; sex, birth weight, length and head circumference; Apgar scores; description of delivery or birth complications including malformations; type and length of hospital stay for mother and infant; delivering physician's and infant physician's names and addresses; method of infant feeding; pregnancy weight gain; and additional exposures and results of prenatal tests occurring since the previous interview.

The outcome interview for spontaneous abortion or elective termination will also be structured and information will be elicited on the following: date and type of outcome; hospital location if applicable; prenatal diagnosis; pathology results if available; and additional exposures and results of prenatal tests occurring since the previous interview(s). The outcome interview for stillborn infants will include all of the above plus information on sex, birth size and autopsy results if available.

Major structural defects, spontaneous abortions, elective terminations, fetal or neonatal deaths occurring in the siponimod-exposed group will be reported to the sponsor within 24 hours of the Research Center staff learning of the event. These reports will be made using the FDA's MedWatch form. The sponsor will be responsible for directly reporting to the FDA and Health Canada for events involving their product according to regulatory guidelines (See Section 9).

7.4.3.4 Medical records and general pediatric evaluation

Upon completion of the outcome interview, each woman will be mailed a packet containing research HIPAA compliant medical records release forms for the delivery hospital, obstetrician, pediatrician, and specialty physician, if applicable. For women whose pregnancies have ended in spontaneous abortion, elective termination or stillbirth, records release forms will be mailed for prenatal diagnosis, pathology or autopsy reports if available. Each woman will be asked to sign the medical records release forms, as well as [redacted] HIPAA Authorization Addendum (if they or their child receives medical care at [redacted]), and to return these authorization documents along with the pregnancy exposure diary form.

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

At one year of age, another research HIPAA compliant medical records release form for the pediatrician or healthcare provider caring for the child is sent to the mother for signature, and the signed form with a standard physical evaluation form is sent to the healthcare provider to request updated information on growth, major structural defects, and any serious or opportunistic infections as defined in this protocol up through one year of age.

7.4.3.5 Dysmorphology evaluation

All live born infants will be eligible for an exam by one of a team of study-dedicated dysmorphologists, led by the study Co-investigator, from the [redacted] The team is made up of licensed pediatricians with subspecialty fellowship training in dysmorphology/genetics. The physical examinations evaluate infants for both major and minor structural defects and provide increased sensitivity for detecting a specific pattern of malformation should one exist. Infants will be examined within the first year of life or as soon as the examination can be practically arranged. The Research Center will group and schedule these follow-up examinations to meet the study criteria of infant age, to maximize physician blinding as to exposure status, and to minimize travel time and expense. The examiner travels to the patient to conduct the examination.

Infant examinations will be conducted using a standard checklist of approximately 130 minor malformations included in a standard physical evaluation form. In addition, with parental consent, digital photographs of the infant will be taken to aid in validating any findings across examiners.

Dysmorphologists will perform these examinations blinded to the exposure or comparison group status of the mothers. Because subjects may have visible evidence of their disease, the use of a disease-matched comparison group allows for preservation of physician blinding. Mothers are asked to sign a consent for medical photographs at the time of the examination. If deemed necessary, the examiners will meet to review photographs of children to assess any patterns that may be identified.

7.4.3.6 Achievement of developmental milestones

When the child is approximately one year of age, the mother will be asked to complete the ASQ developmental screening questionnaire (Squires et al, 2009).

7.4.3.7 Procedure and consequences for subject withdrawal

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

7.4.4 Data collection schedule

Data will be collected according to the schedule described in Table 7-2 below. After oral informed consent, a maternal telephone interview is conducted. Depending on the gestational age at enrollment, up to two additional telephone interviews are scheduled in the second and third trimesters of pregnancy. Written informed consent is requested following the intake interview.

- An outcome telephone interview is planned for 0-6 weeks after delivery
- After the end of pregnancy, research HIPAA compliant medical records release forms for the obstetric provider, delivery hospital, pediatrician, and any specialty care provider for the indicated disease, are sent to the mother for signature. Once the record release forms are received, records are requested from the providers and upon their receipt, data are abstracted.
- A one-year pediatric evaluation release form will be sent to the mother and once signed will be used to request data from the pediatric care provider.
- Between birth and approximately one year of age (or as soon as the examination can be practically arranged), a dysmorphology examination will be scheduled.
- When the child of the participant is approximately one year of age, the participant will be asked to complete the ASQ for her child.

Table 7-2 Timing of Cohort Enrollment, Interviews, Examinations, and Medical Records

	Anytime In Pregnancy	20-22 Weeks' Gestation[b]	32-34 Weeks' Gestation[c]	0-6 Weeks Post-Delivery	0-12 Months Post-Delivery	1 Year Post-Delivery
Referral[a]	√					
Enrollment and Consent[a]	√					

Enrollment Interview[a]	√					
Interim Interview I		√				
Interim Interview II			√			
Pregnancy Outcome Interview and Request for Medical Records				√		
Medical Record Review					√	
Dysmorphology Examination					√	
Developmental Screening / ASQ						√
Pediatric 1-Year Medical Records Request and Review						√

[a]Participants may enroll in the study anytime during pregnancy
[b]If subject is enrolled and Intake Interview is conducted after 18 weeks' gestation, only one interim interview will be conducted during pregnancy at 32-34 weeks gestation
[c]If subject is enrolled and Intake Interview is conducted at 30 weeks' gestation or after, no Interim Interview will be collected

7.5 Study size

Recruitment goals are set at an average of 34-36 subjects per year in each of the 3 groups as shown below in Table 7-3, for a total of 867 subjects in the cohort, and an additional up to 50 subjects in the exposure series (anticipated recruitment not shown in the table), over a 7-year recruitment period. Balance in the cohort numbers will be monitored on a monthly basis, and overall balance addressed by adjusting recruitment activities as needed. It is not possible to predict the number of pregnancy exposures that will occur for a newly marketed medication, or that the recruitment rates will be equal in all years, and therefore, sample size is based on estimates that may require revision as the study progresses.

Table 7-3 Anticipated Recruitment Timetable and Sample Size[a,b]

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Enroll	**Enroll**	**Enroll**	**Enroll**	**Enroll**	**Enroll**	**Enroll**
34 Exposed	36 Exposed	36 Exposed	36 Exposed	36 Exposed	36 Exposed	36 Exposed
34 DMC	36 DMC	36 DMC	36 DMC	36 DMC	36 DMC	36 DMC
34 HC	34 HC	34 HC	36 HC	36 HC	36 HC	36 HC

[a]Disease-matched comparison (DMC)
[b]Healthy comparison (HC)

7.5.1 Determination of sample size

The sample size for this study is not only based on the statistical considerations to address the question of interest but also takes into account the feasibility aspects, prior experience and available literature (Krueger et al 2017) on conduct of pregnancy registries in the MS disease area.

In the three cohorts, approximately 867 pregnant women will be enrolled in US and Canada with a ratio of 1:1:1.

Based on previous experience with MotherToBaby/OTIS Pregnancy Studies, it is estimated that subjects will be an average of 7-10 weeks post-LMP at the time of enrollment. Given this mean gestational timing at enrollment, the anticipated spontaneous abortion/stillbirth rate is 10%, the estimated elective abortion rate is 5%, and the estimated lost to follow-up rate is 5% (Chambers et al, 2016). This will result in known outcomes for approximately 273 pregnancies in each cohort, including 231 pregnancies with at least one live born infant in each cohort at the end of recruitment.

Baseline rates of major structural birth defects, specific patterns of three or more minor structural defects, premature delivery, and small for gestational age are based on previous MotherToBaby/ OTIS studies and on general population data. Rates of spontaneous abortion in the general population are 15-20% (Avalos AL, et al 2012, and Magnus et al 2019). However, since women do not typically enroll in pregnancy registries until after 7-8 weeks' gestation when the highest risk of spontaneous abortion has passed, the baseline estimate is drawn from previous OTIS studies. Table 7-4 gives the minimum detectable effect sizes with 80% power (two-sided significance level 0.05, except as noted below for pattern of minor structural defects), for the comparisons described above. If the disease-matched comparison and the healthy comparison groups are comparable, then consideration will be given to pooling data in the two comparisons cohorts for analysis, as shown in Table 7-5. The current sample size provides 80% power to detect a risk ratio of approximately 4.4 or greater in major structural defects compared to the baseline prevalence of 3% in the comparison groups. This is consistent with the population prevalence of major structural defects of 2.8% in the Atlanta metropolitan area (CDC 2017).

Table 7-4 Sample Size and Detectable Effect Size with 80% Power for Comparison of Exposed Cohort 1 to Unexposed Cohort 2

Endpoint	N per group	Rate in comparison group	Relative risk	Power
Major structural defects[b]	231	3%	3.0	80%
Specific pattern of 3 or more minor structural defects	231	1%	4.6	80%[c]
Spontaneous abortion/still birth	259	10%	1.9	80%

Endpoint	N per group	Rate in comparison group	Relative risk	Power
Preterm delivery	231	10%	1.9	80%
Small for gestational age	231	10%	1.9	80%

[a]All tests are two-sided with alpha = 0.05, based on Fisher's exact test, unless specified otherwise. Calculations conducted using R.
[b]Primary endpoint; among livebirths.
[c]One-sided

Table 7-5 Sample Size and Detectable Effect Size wth 80% Power for Comparison of Exposed Cohort 1 to Unexposed Cohorts 2 and 3 Combined

Endpoint	N in exposed group	N in comparison group	Rate in comparison group	Relative risk	Power
Major structural defects[b]	231	462	3%	2.7	80%
Specific pattern of 3 or more minor structural defects	231	462	1%	4.0	80%[c]
Spontaneous abortion/still birth	259	518	10%	1.7	80%
Preterm delivery	231	462	10%	1.8	80%
Small for gestational age	231	462	10%	1.8	80%

[a]All tests are two-sided with alpha = 0.05, based on Fisher's exact test, unless specified otherwise. Calculations conducted using R.
[b]Primary endpoint; among livebirths.
[c]One-sided

7.5.2 Interim feasibility assessment

An interim assessment to determine the feasibility of continuing the pregnancy registry will be conducted by the Sponsor at the end of three years from the start of the Registry and detailed in the separate SAP. At this interim assessment, data from the following sources will be examined in an integrated manner to determine the feasibility of continuing the pregnancy registry:

- Data from the Registry informing participant demographics (age distribution) and enrollment rate
- Data from secondary analysis of US real world data sources (such as Truven Health MarketScan) informing number and characteristics (age) of siponimod female patients, number of siponimod exposed pregnancies and live birth rate,
- Aggregate US marketing data informing the number and age distribution of US siponimod-exposed women
- Data from PRegnancy outcomes Intensive Monitoring program (PRIM – based on worldwide spontaneous reporting) informing number of pregnancies and outcomes from all over the world including US (for those reports that are not enrolled in the registry)
- Change in treatment landscape with availability of newly marketed drugs safer to use in pregnancy affecting the uptake of siponimod in women of child bearing potential

The integrated analysis of all these data will provide a basis for understanding the siponimod female patient population's characteristics and will help assess whether the scientific question of interest is at all relevant for the siponimod population and whether the Registry will be able

to answer the question in a reasonable timeframe (i.e. study results with targeted sample size with seven years of enrollment).

7.6 Data management

Data will be collected using maternal interview(s), medical records, pregnancy exposure diary, dysmorphology examination data, and ASQ data. Maternal interviews, pregnancy exposure diary, and dysmorphology examination 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. Medical records and ASQ will be received on hard copy forms or electronically. Data from these forms will be extracted and entered into a customized OTIS study database located in the Research Center and developed specifically for the OTIS studies.

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

Access to the database will be controlled by password, with different access privileges assigned to the data entry staff and administrative staff; these privileges are outlined in detail in the OTIS Data Management Guide, Data Entry standard operating procedure (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.

7.7 Data analysis

All analyses will be performed by the OTIS Research Center.

7.7.1 Analysis software

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

7.7.2 Analysis variables

7.7.2.1 Outcome classification for the primary outcome – major structural defects

The method for classifying major structural defects for purpose of analysis has been described by the study investigators and the OTIS Research Group (CDC, 2017; Chambers et al, 2001) and has been used in previous studies conducted by OTIS.

7.7.2.2 Inclusion criteria for the primary outcome – major structural defects

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

- ***Classification of major defects*** will be performed according to the CDC coding list (CDC, 2017) and applied equally across all cohorts in the study. Some major structural defects are known consequences of pregnancy events, such as premature delivery, and are therefore not directly due to drug exposure. For example, isolated patent ductus arteriosus or isolated inguinal hernia in an infant delivered before 36 weeks' gestation are considered consequences of prematurity, and therefore, using CDC coding criteria, none of these defects are counted as major structural defects. Other structural defects, such as club foot or cranial synostosis, could be due to position of the infant in the uterus or could be primary defects initiated earlier in pregnancy. In most cases, it is not possible to know the true onset or etiology of the defect. Therefore, using CDC coding criteria, these anomalies are counted as major structural defects uniformly across all cohorts.
- Using CDC coding criteria, chromosomal anomalies are counted as major structural birth defects. Although it is unlikely that a drug exposure could cause a chromosomal defect, it is not impossible. These major structural defects are counted uniformly across all cohorts in the study. Similarly defects that are identified as due to genetic syndromes are coded uniformly across all cohorts.

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

  With respect to known chromosomal defects or defects determined to represent a known genetic syndrome, a sensitivity analysis is planned, and outlined in the SAP that will exclude these defects.
- ***Analysis subset:*** for the primary outcome of major structural defects, the etiologically relevant window, with rare exceptions, is any exposure in the first trimester and the analysis subset in cohort 1 will be restricted to those with exposure to at least 1 dose of Mayzent from the 4th day post first day of to LMP prior to conception through the end of the first trimester. It is possible that some pregnant women in Cohort 1 could have exposure to Mayzent limited to the second or third trimester, and these would be considered separately. Duration and gestational timing of exposure to siponimod will also be considered.
- ***Time period for identification:*** major structural defects identified up to one year of age by the mother or the healthcare provider/medical record will be included in the primary analysis. Defects identified after that time frame will be described and considered separately.
- ***Confirmation of defects:*** independent confirmation of certain defects will be required. For example, a heart murmur thought to represent a ventricular septal defect

prior to 1 year of age will be included if it is confirmed as a heart defect by cardiac ultrasound. Similarly, a midline cutaneous marker at L2-L3 noted will be included as occult spinal dysraphism only if confirmed by appropriate imaging studies.

- ***Adjudication of major structural birth defects:*** major structural birth defects when reported are first classified by the OTIS study manager once all efforts have been made to obtain adequate information from the mother and infant's healthcare providers. All major structural birth defects are then reviewed in detail by Co-investigators on this study who are clinical teratologists and dysmorphologists/geneticists who are experts in birth defects. The Co-investigator is always blinded to the pregnancy exposure group at the time of the evaluation. If there is a discrepancy in the classification based on these two independent reviews, additional consultation is required for adjudication or classification. This is performed by a member of the Scientific Advisory Board or the Medical Director of the CDCs MACDP. These consultants are also blinded to exposure information at the time of the classification review. After this classification has been completed, at each annual interim and the final Scientific Advisory Board meeting for the study, all major structural birth defects are reviewed. The members of the Scientific Advisory Board, who are experts in major structural birth defects, as part of the review process, may ask for additional information regarding classification of major structural birth defects. However, at the time of the annual report review, the Scientific Advisory Board members are not blinded to exposure. The final adjudication of the classification of major structural defects is made through this multi-step process and all data presentations derived from the study will clearly describe the adjudication process.

7.7.2.3 Exclusion criteria for the primary outcome – major structural defects

- Defects will be excluded based on criteria outlined in the CDC coding list as outlined in Section 7.7.2.2.
- ***Time period for identification:*** structural defects ascertained after 12 months of age will not be included in the primary analysis, but will be considered separately in the context of a possible pattern.
- ***Defects identified in spontaneous abortions/miscarriage, stillbirths or elective terminations/abortions****:* defects identified by prenatal ultrasound or examination of the products of conception following elective or spontaneous abortion/miscarriage or stillbirth will not be included in the primary analysis of the primary outcome due to potential bias involved in non-uniform use of prenatal diagnosis and pathology evaluation for all abortuses; however, these defects will be included in the additional analysis of the primary outcome that includes all defects in the numerator over all pregnancies enrolled in the prospective cohort with known outcome in the denominator (excluding lost-to-follow-up).

7.7.2.4 Outcome classification for secondary outcomes

- ***Spontaneous abortion:*** spontaneous abortion/miscarriage is defined as non-deliberate fetal death which occurs prior to less than 20.0 weeks post-LMP.
- ***Analysis subset:*** the analysis subset for the secondary outcome of spontaneous abortion will be restricted in Cohort 1 to those who were exposed to any dose from

the 4th day post first day of LMP prior to conception to 20 weeks' gestation and enrolled prior to 20 weeks' gestation. The analysis subset for cohorts 2 and 3 will be restricted to those who enrolled prior to 20 weeks' gestation.

- ***Stillbirth****:* stillbirth is defined as non-deliberate fetal death anytime in gestation at or after 20 weeks post-LMP.
- ***Elective termination:*** elective termination/abortion is defined as deliberate termination of pregnancy at any time in gestation. Reasons for elective abortions are captured and are classified as due to medical reasons or social reasons.
- ***Premature delivery:*** premature delivery is defined as live birth prior to 37.0 weeks gestation as counted from LMP (or calculated from first-trimester ultrasound-derived due date if last menstrual period uncertain or more than 1 week discrepant). Elective caesarian deliveries or inductions prior to 37.0 completed weeks will be considered separately.
- ***Preeclampsia / eclampsia:*** preeclampsia or eclampsia reported by maternal interview with confirmation in medical record or report by medical record only is captured.
- ***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 centile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm infants (CDC, 2000; Olsen et al., 2010).
- ***Minor structural defects*:** a minor structural defect is defined as a defect which has neither cosmetic nor functional significance to the child (e.g., complete 2,3 syndactyly of the toes). Minor structural defects will be identified only through the study dysmorphology examination for live born infants using the study-specific checklist.
- ***Postnatal growth deficiency:*** postnatal growth deficiency is defined as postnatal size (weight, length or head circumference) less than or equal to the 10th centile for sex and age using National Center for Health Statistics (NCHS) pediatric growth curves, and adjusted postnatal age for premature infants if the postnatal measurement is obtained at less than one year of age (CDC, 2000).
- ***Screening of Developmental Milestones:*** one or more domains scored as abnormal on the Ages and Stages Questionnaire completed by the mother when the infant is approximately one year of age will define achievement of developmental milestones.
- ***Serious or Opportunistic Infections****:* serious or opportunistic infections are defined as any one or more diagnoses of tuberculosis, x-ray proven pneumonia, neonatal sepsis, meningitis, bacteremia, invasive fungal infection, pneumocysitis, septic arthritis, osteomyelitis, abcess (deep tissue), and infections requiring hospitalization identified in live born infants up to one year of age.

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

7.7.3 General approach to analysis for the cohort study

7.7.3.1 Statistical methods

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

7.7.3.1.1 Analyses of the primary outcome

The primary outcome of interest, i.e. major structural defects, will be estimated in each cohort as a proportion (95% CI) using two denominators i) pregnancies ending in at least one live born infant and ii) pregnancies ending in at least one live born infant, stillborn, spontaneous abortion or elective termination. Data will also be presented by gestational timing of exposure.

For the primary endpoint, the exposure of interest is siponimod exposure at any time from the 4th day post the first day of the LMP prior to conception to the end of the first trimester, whether or not there is continued exposure to siponimod in the second or third trimesters. The primary comparison will be the rate of major structural defects between the siponimod-exposed group and comparison group 1 (disease-matched comparison group) among pregnancies resulting in at least one live born infant. A point estimate of the crude (i.e. unadjusted) risk ratio (RR) of the siponimod-exposed group versus comparison group 1, as well as its 95% confidence interval (CI) will be computed.

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

Due to the observational nature of the study, the above crude estimate of RR will be further adjusted for potential confounders (Rosenbaum, 2002), provided that there are sufficient numbers of events. A complete list of potential confounders, which includes but not limited to the baseline characteristics, will be provided in the SAP for each outcome prior to the final analysis, based on scientific knowledge including literature review.

As a primary approach, following Levenson and Yue, 2013, all potential confounders will be accounted for in the propensity score model.

As a secondary approach, a sensitivity analysis will be considered and the following three criteria applied to identify confounders (Xu et al, 2018, Greenland et al, 1999): 1) by assessing each considered variable in a logistic regression model containing the exposure variable and the outcome variable to determine if inclusion of that single covariate changes the estimate of the odds ratio for exposure by 10% or more; 2) standardized mean differences (SMD) greater than 0.1; 3) association with the outcome with p-value < 0.2 in the unexposed cohort (comparison group 2). Care will be taken not to include those variables that are strongly associated with the exposure variable but only weakly associated with the outcome variable (e.g. instrument like variables) (Brookhart et al, 2006). The confounders identified above will be used to build the propensity score (PS) for exposure (Rosenbaum, 2002).

Balance in the covariate distributions before and after weighting will be assessed by providing the standardized mean differences of all covariates.

The primary analysis will be performed using the PS via inverse probability weighting (IPW).

As secondary analysis, the PS will be used in the so-called outcomes regression (Xu et al, 2018, Vansteelandt et al, 2014), i.e. a logistic regression model will be fitted with major structural defect (Y) as outcome, and exposure (A) and logit of propensity score (L) as regressors. In a second step, standardization will be performed to obtain the estimated causal risk ratio (Hernan and Robins, 2019). The CI for the causal risk ratio will be obtained by bootstrap.

Several sensitivity analyses will be performed for the primary outcome of major structural birth defects. One analysis will exclude those defects thought to be of chromosomal or genetic origin. Exposure to a known human teratogen is already included in the list of potential confounders for the siponimod-exposed group vs. comparison group 1. However, in the case where there are insufficient number of events to consider regression adjustment, a sensitivity analysis will be performed excluding participants with exposure to known teratogens in the siponimod-exposed group and comparison group 1 to address this potential confounder.

As prior knowledge from prenatal ultrasound or diagnostic testing could introduce bias, a sensitivity analysis for the primary outcome of major structural birth defects will be performed stratified on prenatal testing prior to enrollment (yes/no). A second sensitivity analysis is also planned stratified on any abnormal prenatal ultrasound or diagnostic testing prior to enrollment (yes/no). These analyses are described in detail in the SAP.

7.7.3.1.2 Analyses of secondary outcomes

The analysis of spontaneous abortion (SAB) and stillbirth: Only those subjects who are enrolled prior to 20 weeks of gestation are eligible for the analysis of SAB. Since they are not followed from gestational age zero, survival analysis methods will be used to handle left truncation, as well as right-censoring when a subject is lost-to-follow-up prior to 20 weeks' gestation. Left-truncated Kaplan-Meier estimate at 20 weeks' gestation will be used to estimate the SAB rate in each of the cohorts (Tsai et al, 1987). The Cox proportional hazards regression models incorporating left truncation will be used to estimate the hazard ratio (HR) of different cohorts, as well as to obtain the 95% CIs. Stillbirth will be analyzed in a similar fashion. To account for potential confounding, PS methods described above will be applied, where regression adjustment will be used with the Cox model to obtain the adjusted HR.

The analysis of premature delivery: Only those subjects who are enrolled prior to 37 weeks of gestation are eligible for the analysis of premature delivery. These data will be analyzed similarly to SAB, as described above, using survival analysis methods to handle possible right-censoring.

The following will be considered binary endpoints: preeclampsia/eclampsia, small for gestational age (SGA) at birth in weight, height and head circumference, respectively, and growth deficiency at about one year of age in weight, height and head circumference respectively. The analysis of each of these outcomes will be similar to the analysis of the primary outcome, based on all pregnancies resulting in live born infants excluding twins or higher order multiples.

Multiple births will be included in the analyses of minor structural defects, ASQ, and serious or opportunistic infections. These outcome variables will thus likely contain correlated data due to twins or higher order multiples, and the generalized estimating equations (GEE) approach will be used (Liang and Zeger, 1986, Diggle et al, 2002).

7.7.3.2 Missing data

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

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

7.7.4 Year three interim feasibility assessment

At the end of the third year from Registry initiation, feasibility will be re-assessed by the Sponsor. In particular, projections will be made to estimate the number of live births expected 10 years after launch (i.e. at target end date of study). This estimation will be done in an integrated manner taking into account all data sources as described in Section 7.5.2.

As reference, if the projected number of live births after 10 years in the siponimod exposed cohort is less than 100, consideration will be made regarding study discontinuation. Note that these reference thresholds are indicative only and the final decision will be taken based on the totality of evidence accumulated until that point in time.

7.7.5 External comparisons

The overall rate/proportion of major structural defects will be compared with the most recently available rate/proportion published from the MACDP to place the internal comparison group rates in context. However, it should be noted that the MACDP rates for major birth defects represent a population from one urban city that differs in many respects from the sample of women with the indications that are eligible for this study, and the methods of ascertainment do not allow for identification of major structural defects that do not result in hospitalization.

7.7.6 Evaluation for a pattern of major and minor structural defects

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

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

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

7.7.7 Inter-rater reliability

There may be variability in the assessment of minor structural defects among the study dysmorphologists. This will be addressed in three ways:

- The participating dysmorphologists have been working with this study protocol in the existing OTIS Autoimmune Diseases in Pregnancy Project for 10 or more years, and have participated in group training and evaluation exercises. These reliability evaluations involve having examiners independently examine the same infant and comparisons of exam results and measurements are made. These evaluation exercises will continue periodically throughout the duration of this Registry.
- If a pattern of minor structural defects is identified in the interim or final analysis of the study data, photographs of the infants exhibiting this pattern will be independently evaluated by other examiners, and if deemed necessary, affected children can be reexamined by 1 of the other dysmorphologists to ensure agreement.
- In previous studies involving the evaluation of minor structural defects, certain minor structural defects tended to be less reliably detected than others. This raises the possibility of missed identification of a pattern that includes 1 or more of those defects. If the interim reports or final analysis suggest that one or two minor structural defects occur substantially more frequently among exposed infants regardless of examiner, and among these children an additional defect or defects has been identified only by certain examiners, it may be necessary to have infants with those defects re-examined by one of the other dysmorphologists.

7.7.8 Siponimod exposure-series

Women exposed to siponimod during pregnancy but who do not meet the inclusion criteria for the cohort study, will be enrolled into an exposure series group, and their outcomes will be descriptive as there is no appropriate comparison group.

7.7.9 Interim and final study reports

The Registry will develop an annual interim report and any additional *ad hoc* reports with the advice of the Scientific Advisory Board members. Each report will be a composite of the cumulative data to date and will supersede any previous reports. Interim reports will be descriptive only and will include maternal and exposure characteristics for all enrolled, as well as cumulative outcomes by cohort. No statistical comparisons are performed in the interim reports. The final analysis will be conducted when the cohort study has been completed. The study may be terminated at any time based on a variety of considerations. This decision will be considered and a recommendation made upon review by the Scientific Advisory Board and after discussions by the sponsor with relevant health authorities (See Section 11.3.1).

Each interim and the final report for the Registry will provide a summary of the literature regarding siponimod exposure and pregnancy outcomes at the time of the submission of each study report.

7.8 Quality control

Interview, pregnancy diary data, and dysmorphology examination data will be recorded on hard copies of forms and these records will be retained at the Research Center. Medical records and medical records abstraction, and ASQ data will be recorded on hard copy forms or electronically. Data from all study forms will be extracted and entered into a customized database located at the Research Center. The data will be extracted and entered by trained study personnel with experience with this type of information. Entries will be periodically reviewed for logical errors, and a random subset of intake and outcome forms will be double-checked for data entry accuracy. The method and duration of storage of data is addressed in the informed consent. Access to the database will be controlled by password. Hard copies of patient files and participant signed consent forms will be kept in a locked cabinet under the supervision of the study investigators.

7.8.1 Data quality management

The OTIS Research Center will assure database quality processes are followed including review of the data entered into the interview forms by study staff for completeness and accuracy, and in accordance with the data management and validation plans.

7.8.2 Data recording and document retention

The OTIS Research Center will retain study documentation until the end of the study and for a minimum of 15 years after the study completion.

7.8.3 Site monitoring

Not applicable

7.9 Limitations of the research methods

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

Another limitation of the study design relates to the evaluation of spontaneous abortion rates. Rates of early spontaneous abortion, i.e., at 7-9 weeks post-LMP or less, will not be measured in a study that enrolls women after recognition of pregnancy. The study results with respect to spontaneous abortion/miscarriage will be limited to relative risk for late first-trimester and early second-trimester pregnancy loss. The subset of participants who are eligible for this analysis is restricted to those who enroll prior to 20.0 weeks' gestation. Although it has not been the OTIS experience in previous studies, if a high proportion of women enroll in the study after 20.0 weeks' gestation, the statistical power for detecting risks of spontaneous abortion/miscarriage

will be reduced. In addition, if a high proportion of women enroll later in pregnancy, other survival biases may be introduced. A sensitivity analysis by gestational age at enrollment will be performed in order to address these questions.

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

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

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

It is not possible to predict the number of pregnancy exposures that will occur for a newly marketed medication, and therefore, sample size is based on estimates that may require revision as the study progresses. Although all possible measures will be taken to ensure registry awareness and outreach including marketing via websites, social media, print media, scientific conferences, etc., it is known that enrollment rates, particularly in MS pregnancy registries, have been poor (Krueger et al, 2017, Gelperin, et al 2016). Pregnancy registry enrollment rates are subject to drug utilization among pregnant women. Drugs with relatively low use among pregnant women (≤20/100,000 live birth pregnancies) had less successful enrollment in pregnancy registries (Bird et al, 2017). In this study, we have proposed a sample size that accounts for operational feasibility, thereby ensuring generation of data that will provide insights into effects of siponimod on pregnancy outcomes to the patients and prescribers in a timely manner.

Given the Phase III data supporting the siponimod approval for relapsing forms of MS was generated in the SPMS population, as reflected in the clinical studies section of the FDA approved labelling, it may transpire that siponimod is more likely to be prescribed to patients

who are older and with higher disability. Thus there is potential for channeling bias. To the extent that factors such as age and disability differ in exposed and comparison cohorts, these will be considered in adjusted analyses.

It is possible that women in the disease comparison group may have less severe disease than those who enroll in the siponimod exposed group. It is also possible that women in the siponimod exposed group will enroll earlier in pregnancy than either of the comparison groups. The study will monitor disease severity and gestational age at enrollment and discuss any modifications needed in recruitment strategies as the study progresses. Further, all three cohorts rely on volunteers and may not represent the entire population of exposed and unexposed women.

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

The study design has relative strengths with respect to the control of a large number of potential confounders. Information will be collected repeatedly throughout pregnancy on a variety of factors that may be related to exposure and to pregnancy outcome, and the use of a disease-matched 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 one. In addition, each subject is interviewed at several predetermined intervals during pregnancy. Misclassification bias in the outcome is minimized in this study design through the use of 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 OTIS MotherToBaby Pregnancy Studies, and the frequent subject contact, lost-to-follow-up is expected to be less than 5%, and therefore not expected to pose a threat to the validity of study results.

Finally, the small sample size that is projected to be achievable for this Registry has limitations in statistical power. However, the sample size target is similar to that of other pregnancy registries for medications used for relatively rare diseases, and is an important method for early evaluation of a newly marketed medication for safety in pregnancy. The investigators and the Scientific Advisory Board's expert review and comment on the data and the inclusion of evaluation of a pattern of major anomalies are strengths.

8 Protection of human subjects

8.1 Responsibilities of the Investigator and the OTIS Research Center

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

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

The OTIS Research Center is responsible for:

- Local submission(s) complying with data protection rules,
- Any other local submission(s).

8.2 Data protection

The individual participant personal data is incorporated into the study records and the study database, and will be treated in compliance with all local applicable laws and regulations. The Registry makes every effort to assure patient confidentiality within the Registry. When information is distributed to Scientific Advisory Committee members, no contact information or direct patient identifiers are included. Contact information is not shared outside the Registry. No patients are identified in study presentations or publications.

The patient and infant health information is shared in summary form with the Sponsor and the Scientific Advisory Board, in the Registry Annual Interim or Final Reports, but not in publications or presentations. The information contained in line-listing may include dates of exposure, prenatal tests, pregnancy outcome date, and other relevant outcome information.

When archiving or processing personal data pertaining to study participants, the OTIS Research Center will take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

8.2.1 Access to data

- ***Registry Staff:*** The Registry Investigators, data collection and management staff reside at the OTIS Autoimmune Diseases in Pregnancy Research Center located at [redacted]. These personnel, under the supervision of the Investigators, have access to the physical files and electronic data.
- ***Sponsor****:* Sponsor representatives will have access to summary data presented in the interim annual and final reports. Any reports of Serious Adverse Events (SAEs) occurring in siponimod-exposed pregnancies enrolled in the study (major structural birth defects, spontaneous abortions/miscarriages, elective terminations/abortions, stillbirths, and neonatal deaths) not originating at the Sponsor will be reported to the Sponsor through the MedWatch protocol by the Registry staff, regardless of attribution. This data will be utilized by the Sponsor to meet the FDA reporting requirements.
- ***Scientific Advisory Board*** (See Section 11.3.1)*:* The Registry Scientific Advisory Board will receive summary information on pregnancy outcomes for all enrolled in the Registry at each annual interim and final meeting. These reports include specific listings of the specified pregnancy-related SAEs. Contact information is not included in any listings provided. The Scientific Advisory Board, in preparation for the annual meetings, reviews the listings and summary tables. At the meeting, interpretation of results will be discussed and decisions made on the appropriate updates to the Annual Report.

- ***Patient Identifiers:*** Mother and infant names are obtained as part of the informed consent and linked to pregnancy history, exposure and outcome data from maternal interview, medical records, and physical examinations. This personally identified information is maintained securely at the OTIS Research Coordinating Center and is not shared with the Sponsor, Scientific Advisory Board member, or any external parties other than what is required by law. Data summaries for the Sponsor and Scientific Advisory Board will be provided only when data has been stripped of personal identifiers.
- ***Published Data:*** Care is taken to assure that a patient is not identifiable in the data tables published in the Annual Interim or Final Reports, or other publications. No protected health information is included in any published information. Ad hoc requests for Registry information are reviewed and approved by the Registry Investigators with the advice of the Scientific Advisory Committee.

8.3 Regulatory and ethical compliance

8.3.1 Ethical principals

This study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (1995), and the HIPAA (National Institutes of Health, 2002; Andrews et al., 1996).

8.3.2 Laws and regulations

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2007), and with the ethical principles laid down in the Declaration of Helsinki.

8.3.3 Institutional review board

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

The Registry follows the FDA Guidance for Industry for regulatory reporting of serious adverse events (SAEs) to FDA. "The Agency considers pregnancy exposure registry reports (both prospective and retrospective) as derived from active solicitation of patient information." Therefore, the sponsor is responsible for "reporting any serious and unexpected events by regulatory definition and where a reasonable possibility exists that the drug or biological product caused the SAE within 24 hours" (Draft Postapproval Pregnancy Safety Studies; Guidance for Industry, May 2019).

For FDA status reporting the Registry interim report can be appended to the submission as described in the FDA Guidance (Draft Postapproval Pregnancy Safety Studies; Guidance for Industry, May 2019). The Annual Report contains the background, study design, and summary

of the analysis plan. It summarizes the study status and the cumulative data on the Registry to date. In addition, the Registry annual report contains individual line listings for specific outcomes, such as major structural defects, to assist the Sponsors in preparation of their submission. The Registry reports will be current to the most recent data cut-off period.

8.3.4 Participant information and consent

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

The informed consent form will be in compliance with the [redacted] regulatory requirements.

The informed consent forms used in this study, and any changes made during the course of the study, must be prospectively approved by the [redacted] Institutional Review Board (IRB) before use.

The pregnant woman must agree to the oral consent form at the time of enrollment and before completing the intake interview. She must sign an informed consent in order to complete the dysmorphology exam. Each subject will be sent two copies of the written informed consent document following the initial intake interview and requested to sign and return one copy. She must also sign for release of medical information to allow the Registry to obtain information on the pregnancy and the pregnancy outcome from the subject's obstetrician, the hospital of delivery, and any health care specialist, and for the infant from the infant's pediatrician.

The original oral and signed informed consent documents will be maintained by the Registry Office. Original copies of medical record release documents will be retained at the Registry office as well, and the copies will be sent to the institution or physician from whom records are being requested.

Pregnant women under the age of 18 who are eligible for the study and who wish to participate will require written consent of their parent or guardian prior to the initial intake interview and written assent from themselves.

The original oral and signed written informed consent documents and [redacted] HIPAA authorizations (applicable to participants receiving healthcare at [redacted] or [redacted]) will be maintained by the Registry Office. The original research HIPAA compliant medical record release authorizations will be retained at the Registry office as well, and copies will be sent to the institution or physician from whom records are being requested. These medical release documents are in the authorized format required by [redacted] and are compliant with HIPAA regulations.

8.3.5 Participant withdrawal

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

9 Management and reporting of adverse events/adverse reactions

9.1 Safety instructions

9.1.1 Serious Adverse Event

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event.
- Suspected transmission of infectious agent; is any suspected transmission of an infectious agent via a medicinal product (e.g., product contamination).

To ensure patient safety, every SAE as defined in this protocol (see Section 9.2.1), regardless of suspected causality, occurring after the participant has provided informed consent will be reported to the Sponsor within 24 hours of the OTIS Research Center becoming aware of its occurrence. Complications, or progression of the initial SAE will be reported as follow-up to the original episode, regardless of when the event occurs. This report will be submitted within 24 hours of the OTIS Research Center becoming aware of the follow-up information. An SAE that is considered completely unrelated to a previously reported one will be reported separately as a new event.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

9.1.2 Pregnancies

Each pregnancy in a participant exposed to siponimod will be shared with the Sponsor as part of the monthly update listings and processed in the Sponsor's pharmacovigilance system.

If maternal exposed pregnancy information is reported to the Sponsor directly, the reporter's will be asked to participate in the Registry and if possible the call will be immediately transferred to the Registry call center for follow-up. Prior to the call transfer, the Sponsor will collect contact information and basic pregnancy status information in case the call is lost in transfer. In the event the call cannot be transferred, the Sponsor's Patient Safety department should forward the reporter contact information to the OTIS staff only if and after the reporter has provided their verbal consent, in accordance with local law and regulations.

9.1.3 Pregnancy and SAE reconciliation

Pregnancies and SAEs captured within the Registry database will be reconciled with the pregnancy and SAE information submitted to the Sponsor in order to ensure that all relevant information was received. Full details regarding the frequency, methodology and resolution of pregnancy and SAE reconciliation will be detailed in the Registry data management plan.

9.2 Obligations of the OTIS Research Center

9.2.1 Pregnancy and outcomes in a patient exposed to siponimod

During the course of the study, the OTIS Research Center will report to the Sponsor within 24 hours of becoming aware of any of the below listed events occurring in any enrolled pregnancy with siponimod exposure.

The MedWatch form will be used to report these events:

- Pregnancy ending in spontaneous abortion
- Pregnancy ending in stillbirth
- Pregnancy ending in elective termination
- Major structural birth defect in the fetus or infant
- Death of infant
- Death of mother

9.2.2 Other SAEs or AEs notification to the Sponsor

Any other adverse event that is outside the scope of the study, whether serious or not, that the woman or her physician attributes to exposure to siponimod, with the caller's permission, will be transferred to the Sponsor via active forwarding of the reporter to the Sponsor's representative, i.e., "warm transfer". The sponsor will be responsible for directly reporting to the FDA or Health Canada for events listed above involving their product according to regulatory guidelines.

A listing of all reported events described in Section 9.2.1 will be maintained by OTIS and reviewed frequently with the Sponsor throughout and at the end of the study for review and reconciliation.

The Sponsor will report to regulatory authorities in accordance with 21 Code of Federal Regulations (CFR) 314.80, Draft Postapproval Pregnancy Safety Studies; Guidance for Industry. May 2019 and other regulations.

For other reports received from individuals not enrolled in the study or outside the scope of the study, the caller will be given contact information to the Sponsor's safety group.

Other pregnancy related adverse events that are study outcomes, such as preterm delivery, will be summarized in the annual interim and the final study reports.

10 Plans of disseminating and communicating study results

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

10.1 Ownership and use of data and study results

The Annual Interim and Final Reports produced by the study are jointly owned by OTIS and the Sponsor. The raw study data is owned by OTIS, but accessible by Health Authorities directly in case the Sponsor receives the request of an inspection and/or audit from any regulatory agencies.

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

10.2 Publications

Publications including manuscripts on the study outcomes will be prepared by the Registry Investigators and provided to the Sponsor for comment. Manuscripts will be provided for comment at least 90 days in advance of submission. Abstracts and presentations will be provided for comment at least 7 days prior to planned submission.

The Registry will initiate presentations at scientific and professional meetings. The Registry will use these meetings and several other strategies to raise awareness of the Registry. However, the Registry does not identify individual subjects or share its list of providers.

- Interim Reports: An annual interim report will be issued to the Sponsor and the Scientific Advisory Committee on an annual basis in conjunction with the annual Advisory Committee meeting. Each issue will contain historical information as well as new data, and therefore will supersede all previous reports. The report will describe the experience of the ongoing study, summarize all reports to the Registry, and provide descriptive data on pregnancy outcomes in this Registry.
- Website: Information on the Registry is incorporated into the existing OTIS website that includes a description of the Registry, contact information, enrollment eligibility and instructions. The FDA Pregnancy Registry website will continue to list the OTIS Autoimmune Diseases in Pregnancy Project. The Registry will be posted to ClinicalTrials.gov. There are other websites that may provide Registry contact information. The Sponsors' websites will maintain links to the Registry website.
- Abstracts, Manuscripts: The Registry Advisory Committee drafts policy for managing external requests for data analysis or use of information from the Annual Report. Data analyses to support these activities are conducted by the Registry Coordinating Center.

11 Administrative considerations

11.1 Premature discontinuation of the study

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

- Sufficient information has accumulated to meet the scientific objectives of the Registry, i.e., the target sample size is achieved, or
- 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
- Siponimod is withdrawn from the market in North America

In the case that discontinuation or termination of the study is deemed necessary and appropriate, the Sponsor and the Registry Investigators will notify the IRB and FDA, and any other regulatory agencies as needed.

11.2 Audits and inspections by regulatory agencies

The Investigator agrees to allow any competent regulatory authority such as federal agencies (e.g., FDA, etc.), upon their request, to inspect all premises where the project are or have been performed. Upon receipt of the health agency request to inspect its premises as it relates specifically to the performance of the project, the sponsor will be notified promptly.

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

The confidentiality of the data verified and the protection of the study participants will be respected during these inspections.

Any result and information arising from the inspections by the competent authorities will be communicated by the OTIS Research Center to the Sponsor.

OTIS shall take appropriate measures required to take corrective actions for all problems found during the audit or inspections by a federal agency.

11.3 Responsibilities

11.3.1 Scientific advisory board

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

The Scientific Advisory Board is comprised of 1) a Maternal-Fetal Medicine specialist with training in teratology, 2) a geneticist/dysmorphologist with expertise in teratology and birth defects, 3) an epidemiologist with expertise in teratology and birth defects, and 4) a neurologist. The Board is chaired by a designated member, and each member has one vote. A dedicated charter describes roles and responsibilities of the Board members, and members complete conflict of interest disclosures on an annual basis.

Members of the Board provide advice to the Registry Investigators on interpretation of the data and provide advice on strategies for the dissemination of information regarding the Registry.

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

11.3.2 Sponsor

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

11.3.3 Study Investigators and the OTIS Research Center

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

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

12 References (available upon request)

Ammon AL, Galindo C, Li DK (2012) A systematic review to calculate background miscarriage rates using life table analysis. Birth Defects Res.A Clin.Mol.Teratol.; 94 (6):417-423.

Andrews EA, Avorn J, Bortnichak EA, et al (1996) Guidelines for Good Epidemiology Practices for drug, device, and vaccine research in the United States. Pharmacoepidemiol.Drug Saf; 5 (5):333-338.

Bird ST, Gelperin K, Taylor L, et al (2018) Enrollment and Retention in 34 United States Pregnancy Registries Contrasted with the Manufacturer's Capture of Spontaneous Reports for Exposed Pregnancies. Drug Saf; 41 (1):87-94.

Brookhart MA, Schneeweiss S, Rothman KJ, et al (2006) Variable selection for propensity score models. Am.J.Epidemiol.; 163 (12):1149-1156.

CDC. 2000. Individual Growth Charts [Online]. Available at: https://www.cdc.gov/growthcharts/charts.htm [Accessed on 03/2020].

CDC. 2017. Metropolitan Atlanta Congenital Defects Program (MACDP) [Online]. Available at: https://www.cdc.gov/ncbddd/birthdefects/macdp.html [Accessed on 03/2020].

Chambers CD, Johnson DL, Xu R, et al (2016) Safety of the 2010-11, 2011-12, 2012-13, and 2013-14 seasonal influenza vaccines in pregnancy: Birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants, a study from the cohort arm of VAMPSS. Vaccine; 34 (37):4443-4449.

Chambers CD, Braddock SR, Briggs GG, et al (2001) Postmarketing surveillance for human teratogenicity: a model approach. Teratology; 64 (5):252-261.

Diggle PJ, Heagerty PJ, Liang KY, Zeger SL. (2002) Analysis of Longitudinal Data. Oxford University Press.

FDA. Draft Postapproval Pregnancy Safety Studies; Guidance for Industry. Maryland, May 2019

Gelperin K, Hammad H, Leishear K, et al (2017) A systematic review of pregnancy exposure registries: examination of protocol-specified pregnancy outcomes, target sample size, and comparator selection. Pharmacoepidemiol.Drug Saf; 26 (2):208-214.

Greenland S., Robins JM, and Pearl J. S. 1999. Confounding and Collapsibility in Causal Inference Stat. SCI, 14 (1), 29-46.

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

Hernán, M. A.and Robins, J. M. 2019. Casual Inference, Boca Raton, FL, Chapman & Hall/CRC.

Honein MA, Paulozzi LJ, Cragan JD, et al (1999) Evaluation of selected characteristics of pregnancy drug registries. Teratology; 60 (6):356-364.

International Society for Pharmacoepidemiology (2016) Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol.Drug Saf; 25 (1):2-10.
Tsui A, Lee MA (2011) Multiple sclerosis and pregnancy. Curr.Opin.Obstet.Gynecol.; 23 (6):435-439.

Jalkanen A, Alanen A, Airas L (2010) Pregnancy outcome in women with multiple sclerosis: results from a prospective nationwide study in Finland. Mult.Scler.; 16 (8):950-955.

Johnson KA, Weber PA, Jones KL, et al (2001) Selection bias in Teratology Information Service pregnancy outcome studies. Teratology; 64 (2):79-82.

Kobelt G, Berg J, Lindgren P, et al (2006) Costs and quality of life in multiple sclerosis in Europe: method of assessment and analysis. Eur.J.Health Econ.; 7 Suppl 2:S5-13.

Krueger WS, Anthony MS, Saltus CW, et al (2017) Evaluating the Safety of Medication Exposures During Pregnancy: A Case Study of Study Designs and Data Sources in Multiple Sclerosis. Drugs Real World Outcomes.; 4 (3):139-149.

Leen-Mitchell M, Martinez L, Gallegos S, et al (2000) Mini-review: history of organized teratology information services in North America. Teratology; 61 (4):314-317.

Levenson MS, Yue LQ. Regulatory issues of propensity score methodology application to drug and device safety studies. J Biopharm Stat 2013 Jan;23(1):110-21

Liang K and Zeger S (1986) Longitudinal data analysis using generalized linear models. Biometrika, 73.1: 13-22

Magnus MC, Wilcox AJ, Morken NH, et al (2019) Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. BMJ; 364:l869.

National Institutes of Health. 2002. Standards for Privacy of Individually Identifiable Health Information (45 CFR Parts 160 and 164) [Online]. Available at: https://www.hhs.gov/sites/default/files/introduction.pdf [Accessed on 03/2020].

National Institutes of Health. 2003. Protecting personal health information in research: Understanding the HIPAA rule [Online]. Available at: https://privacyruleandresearch.nih.gov/pdf/HIPAA_Booklet_4-14-2003.pdf [Accessed on 03/2020].

Nelson JL, Ostensen M (1997) Pregnancy and rheumatoid arthritis. Rheum.Dis.Clin.North Am.; 23 (1):195-212.

Novartis Pharmaceuticals (2019). Prescribing information for Mayzent (siponimod). East Hanover, New Jersey: Novartis Pharmaceuticals.

Olsen IE, Groveman SA, Lawson ML, et al (2010) New intrauterine growth curves based on United States data. Pediatrics; 125 (2):e214-e224.

Pan W (2000) A multiple imputation approach to Cox regression with interval-censored data. Biometrics; 56 (1):199-203.

Rosenbaum, P. R. 2002. Observational Studies (Second Edition), New York, Springer-Verlag.

Squires, J., Twombly, M. S., Bricker, D.and Potter, L. 2009. ASQ®-3 User's Guide Baltimore, MD, Brookes Publishing.

Tsai W, Jewel N, and Wang M (1987) A note on the product-limit estimator under right censoring and left truncation.; Biometrika, 74 (4): 883-886.

Tsui A and Lee M (2011) Multiple sclerosis and pregnancy. Current opinion in Obstetrics and Gynecology, 23:435-439.

van Buuren S and Groothuis-Oudshoorn K (2011) Mice: Multivariate imputation by chained equations in R. Journal of Statistical Software. 45(3):1-67.

Vandenbroucke JP, von EE, Altman DG, et al (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann.Intern.Med.; 147 (8):W163-W194.

Vansteelandt S, Daniel RM (2014) On regression adjustment for the propensity score. Stat.Med.; 33 (23):4053-4072.

Xu R, Hou J, Chambers CD (2018) The impact of confounder selection in propensity scores when applied to prospective cohort studies in pregnancy. Reprod.Toxicol.; 78:75-80.

13 Annexes

None