NOVARTIS

Global Clinical Epidemiology

FTY720 (fingolimod)

# REDACTED PROTOCOL

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# The Multi-National Gilenya® Pregnancy Exposure Registry in Multiple Sclerosis

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## List of abbreviations

| | |
|---|---|
| BMI | Body Mass Index |
| CDC | Centers for Disease Control |
| eCRF/CRF | Electronic Case Report Form/Case Report Form |
| CRO | Contract Research Organization |
| CVS | Chorionic villus sampling |
| EDC | Electronic Data Capture |
| EDD | Estimated Date of Delivery |
| EMA | European Medicines Agency |
| EUROCAT | European surveillance of Congenital Anomalies |
| FDA | Food and Drug Administration |
| HCP | Health Care Provider |
| ICH | International Council for Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | Institutional Ethics Committee |
| IRB | Institutional Review Board |
| IUGR | Intrauterine Growth Restriction |
| LGA | Large for Gestational Age |
| LMP | Last Menstrual Period |
| MACDP | Metropolitan Atlanta Congenital Defects Program |
| MS | Multiple Sclerosis |
| MTHFR | Methylenetetrahydrofolate reductase |
| NT | Nuchal translucency |
| PIH | Pregnancy-induced Hypertension |
| PROM | Premature Rupture of Membranes |
| SGA | Small for Gestational Age |
| US | United States |

[redacted]

## Amendment 3 (10-Dec-2019)

### Amendment rationale

The rationale for this amendment is to reflect the update in the Gilenya (fingolimod) core datasheet or local product information regarding use of fingolimod in pregnancy.

At the time of writing this amendment, 260 patients were enrolled in the registry.

### Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

Section 1, Section 2, Section 4 and Section 10:

- Update the wording regarding use of fingolimod in pregnancy based on updated Investigator's Brochure Edition 22 and inform physicians to refer to the latest local product information. Update about countries where fingolimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception (eg. European Union, Japan, Russia, Switzerland).
- Add information that fingolimod may increase the risk of congenital malformation in comparison to the general population based on the updated human data.

As per Section 7, a copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, as the changes herein affect the Informed Consent, it is required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

# Summary of Previous Amendments

## Amendment 2 (05-Jul-2012)

### Amendment rationale

The rationale for this amendment is to implement changes required by the FDA clarifying which registry objectives are the main (primary) versus other (secondary) objectives.

In light of the patient enrollment rate being slower than anticipated, one aim of this amendment is to allow remote patient consenting and data collection through the patient in countries where this is acceptable by law. In order to remain compliant with safety reporting duties while reducing site workload, the pharmacovigilance and registry data flows were streamlined.

At the time of writing this amendment, only one patient has been enrolled in the registry.

## Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red~~ font for deletions and red underlined for insertions.

The major changes made to the protocol are summarized in this section. Other minor changes are incorporated directly into the protocol. The major changes included the following:

- Clarifying which registry objectives are the main (primary) (i.e., frequency of malformations) versus other (secondary) objectives.
- Clarifying the inclusion criteria to specify that women must be currently pregnant in order to be eligible to participate in the registry.
- Clarifying the prospective enrollment criteria to indicate that the fetus must not have been assessed by any prenatal tests.
- Updating the pregnancy reporting process to clarify the roles of Novartis, the CRO and the reporting physician.
- A 3-month infant follow-up CRF page was added in order to allow the entire pharmacovigilance responsibility for follow-up on patients/infants participating in the registry to be done through the registry.
- Allowing direct data collection from patients by the reporting physician (without supporting documentation from treating physician) or by CRO staff (US and Canada only).
- Allowing medical record abstraction & data entry performed by CRO staff.
- Differentiating patient registration and enrollment processes for US / Canada and other participating countries.
- Allowing remote patient consenting by the CRO staff acting as registry site in US and Canada.
- Clarifying that patient contact details will only be collected by the registry site.
- The brand name Gilenya was replaced by the international non-proprietary name (INN) fingolimod when the compound is mentioned. The brand name is only used as part of the registry title.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, as the changes herein affect the Informed Consent, it is required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

## Amendment 1 (15-Apr-2011)

The rationale for this amendment was to update the protocol according to the comments received from the FDA on 24th Feb 2011. The major changes were the following:

- Clarifying the enrolment and informed consent timing and procedures for the patient and her infant. In addition to clarifying the different situations in which a patient can discontinue from the study
- In order to limit the lost to follow-up, it will be attempted to get two contact information per patient
- In order to be more in line with common practice, some assessment time points are being relabeled and visit window defined
- To better characterize the weight of the pregnancy outcome, it will be qualified in relation to the gestational age. In addition, the gestational age will be more accurately documented
- In case of spontaneous or elective abortion, Novartis will try to collect pathology reports when those were performed
- To further characterize the infant development, developmental milestones will be captured at the 1 year follow-up where assessed during routine clinical care

At the time of this amendment 1, the registry did not start recruiting patients.

[redacted]

## Executive summary

**Title**: The Multi-National Gilenya Pregnancy Exposure Registry in Multiple Sclerosis.

**Study Purpose**: The purpose of the Multi-National Gilenya Pregnancy Exposure Registry in Multiple Sclerosis (MS) is to continuously monitor, evaluate, and assess for major and minor teratogenic effects in the offspring of women exposed to fingolimod before (up to 8 weeks before last menstrual period (LMP)) and during pregnancy in routine clinical practice. The overall aim is to collect and evaluate data on maternal, fetal, and infant outcomes and compare it with reference populations.

**Objectives**:

The main (primary) objective of the registry is:

- To describe the overall frequency of major and minor congenital malformations associated with exposure to fingolimod during pregnancy.

The other (secondary) objectives of the registry are:

- To describe the frequency of specific types of major and minor congenital malformations associated with exposure to fingolimod during pregnancy;
- To characterize the nature of pregnancy and other fetal outcomes associated with exposure to fingolimod during pregnancy such as spontaneous abortions, stillbirths and elective terminations;
- To describe the occurrence of physical developmental delays as well as adverse effects on immune system development in infants around one year of age associated with exposure to fingolimod during pregnancy.

**Patient Population**: The targeted patient population is pregnant women with MS exposed to fingolimod during pregnancy or up to 8 weeks before last menstrual period. Reference data will come from general established surveillance systems, the medical literature and potentially other existing registries that include patients with MS. Furthermore, frequency of congenital anomalies among women with first trimester exposure will be compared with risks of congenital anomalies among women with second and third trimester exposure if enough data is available.

**Inclusion Criteria**:

- Any woman with a diagnosis of MS
- Any woman currently pregnant
- Exposure to fingolimod during pregnancy or up to 8 weeks before LMP
- Signed informed consent

**Exclusion Criteria**: None.

**Study Design**: The Gilenya Pregnancy Exposure Registry is a (at least) six-year, multi-national, prospective observational study. It is designed as a prospective, observational registry collecting data regarding fingolimod exposure during pregnancy and maternal, fetal and infant outcomes. Early and later term pregnancy outcomes will be solicited at selected gestational time points and post-partum (around the time of the estimated date of delivery).

[redacted]

Structural and functional congenital anomalies identified in the perinatal period through one year of life will be collected and classified, and developmental status in infants will also be recorded. In order to reduce the bias that may occur when some outcome information is known prior to enrollment, women should be enrolled in the registry as soon as their pregnancy is known, preferably in the first trimester before the condition of the fetus has been assessed through targeted prenatal testing.

*Baseline Assessment:* Maternal information, including demographics, prenatal test results, information on fingolimod and other exposures, medical and obstetrical history.

*Mid 2$^{nd}$ trimester follow-up:* Any additional prenatal testing, maternal (and fetal) outcomes, updated exposure information.

*Post-partum follow-up:* Maternal outcome, gestational outcome, type of major and minor malformation, obstetrical complications.

3 month follow-up: Infant vital status, any major or minor malformation(s) diagnosed since the initial birth report or any other conditions noted at or around birth (e.g., positional deformities, features of prematurity, chromosomal abnormalities, genetic disorders).

*One year follow-up:* One additional follow-up will be conducted around the first birthday of the child to collect data on the physical and immune system development status of the infant.

[redacted]

# 1 Background and rationale

Multiple Sclerosis (MS) is a chronic, demyelinating, immune-mediated disease of the central nervous system characterized by inflammation and destruction of myelin and axons (Trapp et al 1998, Sospedra and Martin 2005). Typically recurrent acute episodes (relapses) of neurological symptoms, which are followed by a complete or partial recovery, can be observed during the relapsing remitting multiple sclerosis disease course (Keegan and Noseworthy 2002). Globally, the median estimated incidence of MS is 2.5 per 100,000 (ranging from 1.1 to 4.0 per 100,000) and the median estimated prevalence is 30.0 per 100,000 (ranging from 5.0 to 80.0 per 100,000) (WHO 2008). These estimates vary depending on the country or specific population (Rosati 2001).

In the US, 3,030 infants with birth defects per 100,000 live births were reported by the Centers for Disease Control (CDC 2010). The European surveillance of congenital anomalies (EUROCAT) reported a prevalence rate of 2334.2 per 100,000 live births (EUROCAT 2010). Worldwide about 6% of all newborn infants have serious birth defects of genetic or partially genetic origin and the annual prevalence of congenital malformations was 3,650 per 100,000 births (Christianson et al 2006). There is evidence to support that there is no discernible effect of MS on the risk of adverse pregnancy outcomes, including spontaneous loss, still birth, delivery complications, low birth weight, abnormal head circumference and congenital malformations (Dahl et al 2005, Houtchens 2007, Dahl 2008, Kelly et al 2009).

Fingolimod (FTY720) Gilenya® is a new chemical entity for once daily oral administration intended for the treatment of MS, which has demonstrated very good efficacy, both in placebo- and interferon beta-1a intramuscular controlled clinical trials (Cohen et al 2010, Kappos et al 2010).

In animal models it was shown that fingolimod and its metabolites cross the placental barrier in pregnant rabbits (5.0 mg/kg orally) to a limited extent. The radioactivity concentrations in the fetuses were approximately 4-fold lower than in maternal blood. In rats, fingolimod increased post-implantation loss, and decreased the number of viable fetuses. In rabbits, fingolimod increased embryo-fetal mortality, decreased the number of viable fetuses and induced fetal growth retardation. The receptor affected by fingolimod (sphingosine 1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. Fingolimod was teratogenic in rats, including persistent truncus arteriosus, ventricular septal defect [FTY720D-Summary of Safety Information]. The embryo-fetal effects in rats and rabbits occurred at maternal exposures similar to human therapeutic exposures. Available human data (post-marketing spontaneous reports and data from the Gilenya (fingolimod) pregnancy registry) suggest that use of fingolimod is associated with an increased prevalence of major congenital malformation in comparison to the general population.

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with fingolimod.

As of 28-Feb-2019, in more than 600 prospective pregnancies with live births, still births or termination of pregnancy due to fetal anomaly with maternal exposure to fingolimod during pregnancy that were reported in post-marketing setting, the proportion of major congenital

malformations was approximately 5% (Investigator's Brochure, Edition 10, 2019). The prevalence of major congenital malformation in the general population is reported to be 2 to 3% in the European Union (EUROCAT) and 2 to 4% in the US (FDA Guidance for Industry, 2014).

The pattern of malformation reported for fingolimod is similar to that observed in the general population, wherein the common major malformations are:

- Congenital heart disease such as atrial and ventricular septal defects, tetralogy of Fallot
- Renal abnormalities
- Musculoskeletal abnormalities

There is no evidence of clustering of specific birth defects with fingolimod. Available human data (post-marketing spontaneous reports and the Gilenya (fingolimod) pregnancy registry) suggest that use of fingolimod is associated with an increased prevalence of major congenital malformation in comparison to the general population. In some countries (e.g European Union, Japan, Russia, Switzerland), fingolimod is contraindicated in the use relating to pregnancy. Latest local fingolimod product information and educational material for these countries should be referred to for guidance and more information.

This pregnancy exposure registry is obtaining prospectively and systematically collected data on the potential pregnancy outcome and fetal effects associated with exposure to fingolimod during pregnancy, as opposed to relying on spontaneous adverse event reports. Therefore, the aim of this multi-national pregnancy exposure registry is to continuously monitor, evaluate, and assess any maternal, fetal, and infant outcomes in women treated with fingolimod during pregnancy in routine clinical practice in order to inform treating physicians and patients regarding the risk of major and minor malformations and other adverse pregnancy, maternal, fetal and infant outcomes.

## 2 Objective

The overall goal of the Gilenya pregnancy exposure registry is to prospectively collect and evaluate safety data on Gilenya exposure immediately before (up to 8 weeks before last menstrual period (LMP)) and during pregnancy and associated pregnancy outcomes to compare the maternal, fetal, and infant outcomes in the registry to the background frequency from reference populations.

The main (primary) objective is:

- To describe the overall frequency of major and minor congenital malformations associated with exposure to fingolimod during pregnancy.

The other (secondary) objectives are:

- To describe the frequency of specific types of major and minor congenital malformations associated with exposure to fingolimod during pregnancy;
- To characterize the nature of pregnancy and other fetal outcomes associated with exposure to fingolimod during pregnancy such as spontaneous abortions, stillbirths and elective terminations;

[redacted]

- To describe the occurrence of physical developmental delays as well as adverse effects on immune system development in infants around one year of age associated with exposure to fingolimod during pregnancy.

The findings from the Gilenya pregnancy registry will be used to give healthcare providers (HCP) important information for counseling patients treated with fingolimod who become or want to get pregnant.

# 3 Study design

The design of the pregnancy exposure registry is consistent with relevant guidelines and recommendations (FDA 2002, EMEA 2005, Gliklich and Dreyer 2007, Andrews et al 2008). The pregnancy exposure registry is designed as a (at least) six-year multi-national prospective observational study including approximately up to 500 pregnant women that are exposed to fingolimod any time during their pregnancy or shortly before their pregnancy (up to 8 weeks before LMP). Inclusion of exposures occurring up to 8 weeks prior to LMP is based on the relatively long half-life of fingolimod. Paternal exposure pregnancy cases will not be included. The registry is voluntary and any currently pregnant woman with MS exposed to fingolimod, as defined above, is eligible for enrollment.

Data will be collected during pregnancy (e.g., risk factors, other exposures and pregnancy complications) as well as at the end of pregnancy for pregnancy, maternal and fetal outcomes. Information on pregnant women treated with fingolimod will be provided to the registry prospectively. The HCP will be advised to recommend that any pregnant women exposed to fingolimod enroll in the registry. To increase validity of the data, specific efforts will be made to enroll women as early in their pregnancy as possible.

Where allowed by local regulations, it will also be possible for women treated with fingolimod to pre-register for the registry themselves. The data will then be collected by contacting the respective HCP(s) after the patient has signed the informed consent form. All reports of pregnancy in women who are either not eligible for inclusion in the registry or decline to participate, or originating from sites that have not yet been activated for participation will be forwarded to Novartis Drug Safety & Epidemiology for appropriate follow-up as spontaneously reported events.

To maximize enrollment of eligible pregnant women, recruitment procedures and promotion of the registry will be undertaken, including providing information on how to contact the registry on the fingolimod package insert and personal mailings to specialists wherever legally possible. Furthermore, wherever feasible, information on the registry will be made available to the MS societies, nurse associations and to other relevant fora.

Infants born to the enrolled women will be followed up twice: first after 3 months of age to assess changes since the post partum visit and second around the first birthday to document physical and immune system development and to capture any anomalies not previously identified. Information about the general development (weight, size, head circumference), medical conditions (e.g. number of severe infections leading to hospitalization) and developmental milestones will be recorded in a standardized manner. A follow-up time of 12 months is consistent with regulatory body guidelines and many general screening programs in

[redacted]

various countries (e.g., Germany). Where allowed by local regulation, enrolled women will be contacted at approximately six months after giving birth in order to update relevant contact and HCP information, and minimize loss to follow-up.

The registry will be managed globally by a Contract Research Organization (CRO). All data will be collected and entered by the sites directly into an electronic data capture (EDC) system via electronic case report forms (eCRFs) where feasible; otherwise, paper CRFs will be used and entered into the EDC by the CRO. Paper CRFs may be submitted to the CRO by mail, scanned and emailed or secure fax (preferred). There will also be the option for physicians to provide the data over the phone to the CRO staff for data entry into the registry eCRFs.

## 3.1 Study population

The registry is designed for open enrollment of all patients meeting the inclusion criteria described in Section 3.1.1. In order to reduce the bias that may occur when some outcome information is known prior to enrollment, women should be enrolled into the registry as soon as their pregnancy is known, preferably in the first trimester before the condition of the fetus has been assessed through prenatal testing, including ultrasound, amniocentesis, genetic testing, nuchal translucency screen (NT screen) and chorionic villus sampling (CVS). Targeted prenatal testing is considered to be an outcome assessment since this testing may provide knowledge about structural malformations. First trimester dating ultrasounds are not generally considered as potential assessment of outcome.

Cases for which the condition of the fetus is known as a result of prenatal testing at the time of enrollment will be considered retrospective cases. While such cases will be eligible for enrollment and data collection will be similar as for prospective cases, retrospective cases will be analyzed separately to reduce any potential bias resulting from potential knowledge of outcome at the time of enrollment. The time of enrollment is defined as the time when the patient signs the informed consent.

The criteria for **prospective enrollment** are:

- The condition of the fetus has NOT been assessed through prenatal testing such as targeted ultrasound, amniocentesis, NT screen or CVS at the time of enrollment and the outcome of the pregnancy is NOT known at the time of enrollment.

The criteria for **retrospective enrollment** are:

- The condition of the fetus has been assessed through prenatal testing such as targeted ultrasound, amniocentesis, NT screen or CVS at the time of enrollment and/or the outcome of the pregnancy is known at the time of enrollment.

### 3.1.1 Eligibility

Patients eligible for enrollment in this study must fulfill all of the following criteria:

**Inclusion criteria**:

- Any woman with a diagnosis of MS
- Any woman currently pregnant
- Exposure to fingolimod during pregnancy or up to 8 weeks before LMP

[redacted]

- Signed informed consent

**Exclusion criteria**:

- None

A pregnancy where fetal exposure to fingolimod is possible but cannot be confirmed because date of conception and/or the dates of fingolimod exposure are unknown will be eligible for enrollment, but for analysis purposes categorized as case with "unconfirmed exposure".

### 3.1.2 Patient withdrawal and discontinuation from registry

Patients may withdraw consent provided at enrollment and discontinue participation in the registry at any time, with no effect on their medical care or access to treatment. If a patient withdraws from registry participation, any known reason for withdrawal is to be documented in the database. All information already collected as part of the registry will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient for the purpose of this registry.

Patients will be considered prematurely discontinued from the registry in the following cases:

- the patient has specifically requested to withdraw from the registry
- the patient is lost to follow-up
- the patient died

For live births, premature discontinuation from the registry is considered in the following cases:

- the mother has specifically requested to withdraw her infant from the registry
- the mother is lost to follow-up
- the mother died
- the infant died

Data to be collected at the end of patient participation will include all pregnancy and infant outcome follow-up data available at the time of discontinuation, as well as the reason for discontinuation.

### 3.1.3 Selection of sites and physicians

The intent of the registry is to actively pursue and capture as many as possible of the fingolimod maternally exposed pregnancies identified; therefore, there is no limit to the number or type of physicians and/or patients that may contribute data to the registry.

## 3.2 Exposure of interest

The exposure of interest is fingolimod exposure during pregnancy or immediately prior to becoming pregnant (up to 8 weeks before LMP).

## 3.3 Study endpoints

One outcome of interest is major malformations, which are defined as any structural defect with surgical, medical, or cosmetic importance recognized. In addition, data on minor

[redacted]

congenital anomalies and overall pregnancy outcomes will be collected i.e., spontaneous fetal loss, stillbirth and induced abortion. Complications during pregnancy will also be recorded. Data on potential adverse effects on the physical and immune system development of the offspring, and any other adverse pregnancy and maternal outcomes will be collected. If the pregnancy outcome is a live birth involving a congenital anomaly or other outcome for which there is evidence of a congenital anomaly, patient data will be forwarded to the independent registry clinical reviewer (e.g. a teratologist) who will complete a congenital anomaly evaluation.

The following physical features will be collected but will not be recorded as major malformations:

- Minor anomalies, i.e., anomalies with no serious medical or cosmetic consequence to the child.
- Positional deformities, i.e., a positional deformity that usually normalizes spontaneously after about 3 months of age, e.g., abnormal head shape, torticollis.
- Features of pre-maturity.
- Chromosome abnormalities.
- Genetic disorders.

## 3.4 Data collection

All data will be collected on eCRFs (or on paper CRFs and centrally entered) and stored in the EDC system. The EDC system is designed with a customizable workflow which will present the visit specific forms to the user.

- For data capture, the eCRFs will correspond to six different time-based assessment periods: baseline, mid-second trimester, post-partum (up to 3 months after estimated date of delivery (EDD)), 3 month follow-up (from 3 months after EDD up to infant age 9 months), one year follow-up (10 to 14 months), and discontinuation (including early termination/end of study).
- Additionally, separate forms are used for the reporting of an adverse event, maternal conditions, prenatal testing, congenital malformation, healthcare provider log and concomitant medications.

If the patient's HCP is not able to provide the information needed, any information known by the mother will be solicited directly from her by the registry team (where allowed by local regulation) and recorded as medically unconfirmed by a HCP. For any safety outcomes all efforts will be made to obtain a confirmation by a HCP.

The data to be collected in each CRF are specified in Sections 3.4.1 to 3.4.6 and summarized in Table 3-1 for the patient/fetus and Table 3-2 for the infant.

[redacted]

**Table 3-1 Recommended schedule of data collection: Maternal and fetal exposures and outcomes**

| Visit | Baseline | Mid-2nd Trimester | Post-partum | End of Registry or Premature Discontinuation |
|---|---|---|---|---|
| Window | At enrollment | 21 weeks gestational age +/- 2 weeks | Up to 3 months after EDD | At the end of patient's participation |
| Informed Consent | X | | | |
| Maternal demographics | X | | | |
| MS disease and treatment history | X | | | |
| Gestational age at enrollment (by LMP or ultrasound) | X | | | |
| Obstetrical history, including previous pregnancy outcomes and sibling information | X | | | |
| Relevant maternal/paternal family history of pregnancy complications/congenital abnormalities | X | | | |
| Medical history/newly diagnosed conditions of mother | X | | | |
| Fingolimod dosing and administration | X | X | X | X |
| Prenatal test results | X | X | X | X |
| Other exposures, including lifestyle factors and concomitant medications | X | X | X | X |
| Participation in fingolimod studies* | X | | | |
| Obstetric and delivery complications | | | X | X |
| Pregnancy outcome, including gestational age at outcome | | | X | X |
| Major and minor malformations | X | X | X | X |
| Adverse events | X | X | X | X |
| Reason for premature discontinuation | | | | X |

* Fingolimod clinical trials and any non-interventional fingolimod studies.

[redacted]

**Table 3-2 Recommended schedule of data collection: Infant outcomes**

| Visit | Post-partum | 3 months Follow-up | One Year Follow-up | Premature Discontinuation |
|---|---|---|---|---|
| Window | Up to 3 months after EDD | EDD + 3 months to infant age 9 months | Infant age 10 to 14 months | At the end of infant's participation |
| Informed consent for infant | X | | | |
| Infant outcome details | X | X | X | X |
| Major and minor malformations** | X | X | X | X |
| Infant height, weight and head circumference | X | | X | X |
| Infant medical conditions, including testing/procedures and diagnoses | X | | X | X |
| Breastfeeding history and duration | | | X | X |
| Neurodevelopmental milestone status | | | X | X |
| Adverse events | X | X | X | X |
| Reason for early discontinuation | | | | X |

** In addition to occurrence, detailed information on major and minor malformations (e.g., diagnostic or pathology results) are to be collected when available.

### 3.4.1 Enrollment/baseline

Patients will be formally enrolled by a HCP or by the CRO (refer to Section 6.1 for further details regarding enrollment procedures). A patient is defined as being enrolled once she has signed the informed consent form.

Once a patient has provided their informed consent for participation in the registry, a non-patient identifying registry ID number will be assigned to each participant. To ensure confidentiality, no direct patient identifying information will be included in the registry database used for data collection of clinical information. Patient and HCP(s) contact details which were collected during the enrollment process will be kept separate and protected by the site for follow-up purposes only. Examples of patient contact information details include two forms of contact for the eligible patients as well as the contact information of two other persons who know the patient (e.g., a family member or a friend living outside of the patient's home).

Once enrolled, patients will be observed until the end of the planned participation or termination of the registry.

The following baseline information will be collected and reported to the registry:

- Documentation of informed consent.
- Date of contact
- Reporter type (e.g., patient, neurologist, obstetrician, midwife, other HCP).

[redacted]

- Multiple sclerosis disease history, including years since onset of MS symptoms, years since MS diagnosis, initial course (e.g., relapsing remitting, secondary progressive), previous exposure to disease-modifying therapies.
- Fingolimod exposure including dosing and dates of administration including start and end dates of dosing period during various trimesters of pregnancy.
- Demographic characteristics, including maternal age at last menstrual period (LMP) and ethnicity.
- LMP and EDD (preferably by earliest ultrasound).
- Maternal height and weight (for calculated body mass index (BMI)).
- Gestational age at enrollment (by LMP and/or ultrasound, if available).
- Targeted prenatal testing performed (yes/no).
- Date and results of any prenatal tests performed such as ultrasound, amniocentesis, serum markers, NT screen and CVS.
- Significant maternal medical conditions other than MS (e.g., diabetes, hypertension, cardiovascular disease, epilepsy or seizure disorder, depression, hepatitis, thyroid disease, concomitant autoimmune disease).
- Obstetrical history, e.g., earlier pregnancies and outcomes if not primagravida, including information about siblings.
- Relevant maternal/paternal family history of pregnancy complications/congenital abnormalities.
- Other exposures, such as recreational drugs, including alcohol use, cigarette smoking and illicit drugs, as well as dosage and dosing regimen of other medical products used, including prescription products, over-the-counter products, dietary supplements, vaccines, and insertable or implantable devices.
- Information on whether the patient is participating in any other fingolimod studies (including clinical trials and non-interventional studies).
- Contact information for the mother's HCP(s).

### 3.4.2 Mid-2nd trimester (21 weeks gestational age +/- 2 weeks)

For patients enrolled during the first trimester, the following data will be collected during the mid-second trimester. For patients enrolled after week 19, baseline data will be collected and mid-2nd trimester data collection is not needed.

- Date of contact/follow-up.
- Gestational age in weeks and days at time of follow-up by ultrasound or LMP.
- Information on any prenatal tests such as ultrasound, amniocentesis, serum markers, NT screen or CVS.
- Major or minor malformations identified.
- Pregnancy outcome (if not ongoing).
- If elective termination, specify primary reason (i.e., identified anomaly, increased risk of anomaly, non-medical reasons).
- Spontaneous abortion.

[redacted]

- Gestational age at pregnancy outcome (weeks).
- Updated fingolimod exposure and concomitant medication exposure information.

### 3.4.3 Post-partum (up to 3 months after expected delivery date)

At the time of the estimated delivery the patient's registry site will be contacted by the registry team and asked to provide the necessary follow-up information. Although it is anticipated that data regarding pregnancy outcome will be provided by an obstetrician or other perinatal HCP, it may also be provided by the patient's neurologist, the patient herself or other physician if necessary. The patient's primary HCP may change during the course of follow-up and data may be collected from multiple sources. In order to prevent loss to follow-up and incomplete reports, alternative sources of information will be pursued as required, if contact information is available.. As with all other time points, no direct patient identifiable information such as name and address will be reported to the registry. Baseline information and outcome as well as other follow-up assessment will be linked using the unique patient ID.

The following data will be collected post-partum:

- Documentation of informed consent for the infant.
- Date of contact, contact information (separate database) and specialty of HCP(s) providing information.
- Pregnancy outcome (term or preterm live birth, elective termination, fetal death).
- Date of pregnancy outcome or gestational age in weeks.
- If elective termination, specify primary reason (identified anomaly, increased risk of anomaly, non-medical reasons).
- Obstetric and delivery complications (preterm delivery, premature rupture of membranes (PROM), preeclampsia/severe pregnancy-induced hypertension (PIH)/proteinuria, gestational diabetes, intrauterine growth retardation (IUGR) and so on).
- Live births: whether single or multiple births (if multiple, number of fetuses).
- For each infant:
  1. Infant gender
  2. Birth length (in or cm)
  3. Gestational age (weeks, days)
  4. Birth weight (lbs/oz or grams)
  5. Head circumference (in or cm)
  6. Apgar scores (1, 5 and 10 minutes)
- Tests/procedures performed and any associated diagnoses.
- Infant vital status (alive / deceased).
- Presence of major congenital malformations, e.g., heart defect, spina bifida, club foot deformity, cleft palate.
- Presence of minor congenital malformations (i.e., anomalies with no serious medical or cosmetic consequence to the infant).
- Other conditions noted at or around birth (e.g., positional deformities, features of prematurity, chromosomal abnormalities, genetic disorders).

[redacted]

- Neonatal illnesses, need for resuscitation/hospitalization/neonatal intensive care and drug therapies administered.

### 3.4.4 Three-month follow-up (infant age 3 to 9 months)

The following data will be collected at the three-month follow-up:

- Date of contact, contact information (separate database) and specialty of healthcare provider(s) providing information.
- For each infant:
  1. Infant vital status (alive / deceased)
  2. Any major or minor malformation(s) diagnosed since initial birth report
  3. Other conditions noted at or around birth (e.g., positional deformities, features of prematurity, chromosomal abnormalities, genetic disorders).

### 3.4.5 One-year follow-up (infant age 10 to 14 months)

The following data will be collected at one-year follow-up for each infant:

- Date of contact
- Any major or minor malformation(s) diagnosed since initial birth report.
- Infant vital status (alive / deceased).
- Infant height, weight and head circumference.
- History of significant diseases, including any requiring hospitalization and medications.
- Relevant testing/procedures performed and any associated diagnoses (if a specific diagnosis is not possible or available, the results/findings of the testing should be reported for completeness).
- Potential adverse effects on immune system development (e.g., serious infections requiring hospitalization).
- Breastfeeding history and duration (months).
- Developmental milestone status.
- Other relevant testing/procedures performed and any associated diagnoses.

### 3.4.6 End of Registry / Premature Discontinuation

All patients should have either the post-partum or the end of registry data collection (Table 3-1) depending on pregnancy outcome. The end of registry data collection will also be done if the patient discontinues from the registry prematurely.

For all infants who did not have the One-Year Follow-up data collection completed the data will be collected at the time of premature discontinuation of the infant's participation.

### 3.4.7 Targeted follow-up

If one or more major or minor malformations are noted, it may be necessary to collect additional information. Signed release forms will be obtained by the enrolling HCP from the mother to acquire maternal and pediatric medical records and permission to contact the appropriate HCP, i.e., obstetrician/gynecologist, and/or pediatrician. Medical records will

allow for case verification. Each potential case will undergo clinical review to confirm status as a congenital anomaly case and to ensure the anomaly (or anomalies) are coded appropriately (i.e., accurately represent the defect or underlying diagnosis). Many terms are used clinically for the same structural or functional defect; therefore, the coding and grouping of anomalies is the key to a meaningful analysis of results. The clinical reviewer will determine what, if any, structural or functional abnormalities are present, if these are minor or major malformations and if there is additional information required to assess the case (e.g., pathology reports, medical records, assessment by neonatologist/pediatrician).

### 3.4.8 Lost to follow-up

Registry pregnancy reports will be considered complete for live births when data regarding the pregnancy, neonatal and infant outcomes through one year have been received. For pregnancies that do not result in a live birth, follow-up is complete once pregnancy outcome details have been provided.

At enrollment (and as part of the informed consent process), patients will be asked to provide their contact details as well as the contact details of at least two other people (e.g., a family member or a friend living outside of the patient's home), in case the patient is not reachable and an alternate contact is needed. Patients will be contacted by email (if provided), then by telephone. If the patient cannot be reached by these modalities, then the alternate contact(s) will be contacted by the registry site.

For registry purposes, patients will be considered lost to follow-up if any time-based assessment is missed and the corresponding data have not been received by the registry after making additional follow-up attempts using all contact modalities available (e.g., phone, fax, registered receipt letter). At least 3 attempts will be made up to 4 months after the expected date of the missed assessment. Patients will be considered lost to follow-up 30 days after the last contact attempt. The case will be re-opened should additional information be later obtained. All HCPs on record will be contacted prior to considering the patient lost to follow-up. All data collected prior to considering the patient lost to follow-up will be used for analysis and reporting purposes, to the extent possible. The date of discontinuation is considered the date of the last successful contact with the patient.

### 3.4.9 Study discontinuation

Upon agreement with relevant health authorities, Novartis has the right to prematurely terminate this registry at any time. The potential reasons to discontinue this pregnancy registry include, but are not limited to:

- Accumulation of sufficient information to meet the registry's scientific objectives.
- Feasibility [e.g., low prevalence of exposure, poor enrollment (due to patient or physician inability to participate), high rate of loss to follow-up].
- Availability of alternative sources of data suitable to meet the scientific objectives.

## 3.5 Comparison groups

The findings in the proposed pregnancy exposure registry will be compared to external comparison groups, e.g., data collected by external investigators including data made

[redacted]

available from other registries that include pregnancy exposure and outcome information. External comparison groups will include the general surveillance systems such as the National Center on Birth Defects and Developmental Disabilities, U.S. Centers for Disease Control (CDC), or the National Birth Defect Prevention Network, EUROCAT and possibly other national surveillance groups.

The CDC's Metropolitan Atlanta Congenital Defects Program (MACDP) is a population-based birth defect surveillance system that monitors all major birth defects in five counties of the metropolitan Atlanta area (Clayton, Cobb, DeKalb, Fulton, and Gwinnett) with approximately 50,000 annual births from a population of about 2.9 million. MACDP, which started in 1967, acts as the model for many state-based programs and as a resource for the development of uniform methods and approaches to birth defect surveillance, and will be used as the comparator for U.S. based cases. The MACDP uses a 6-digit coding system for birth defect data that is based on an ICD-9 derived system established by the British Pediatric Association. Therefore the data remains compatible with hospital and other data sets, while providing additional specificity for most birth defect codes, thereby facilitating the use of the MACDP as a valid external comparator.

European surveillance of congenital anomalies (EUROCAT) is a European network containing data from population-based registries for the epidemiologic surveillance of congenital anomalies, and will be used as the external comparator group for European cases. EUROCAT, which started in 1979, includes 43 registries from 20 countries covering 29% of the European birth population with 1.5 million births surveyed per year.

There is currently no evidence that MS itself is associated with an increased risk of adverse pregnancy outcomes (i.e., miscarriage, stillbirth or congenital malformations, details see Dahl et al (2005), Dahl (2008), Dahl et al (2008), Kelly et al (2009) and Houtchens (2007), therefore comparison data from large surveillance systems or national statistics should allow a valid comparison. Furthermore, as the highest risk for major malformation is related to exposure during the first trimester, the frequency of congenital malformations among women with first trimester exposure will be compared to women with second and third trimester exposure (if sufficient data are available) to allow an additional internal comparison. Relevant published data sources will be used to evaluate the frequency of other adverse pregnancy outcomes in the exposed population.

# 4 Safety

## 4.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after signing the informed consent even if the event is not considered to be related to fingolimod. Medical conditions/diseases present before signing the informed consent are only considered adverse events if they worsen after signing the informed consent. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each encounter with the patient. Adverse events also may be detected when they are

volunteered by the patient during or between visits or through routine physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. Severity grade [mild, moderate or severe]
2. Relationship to fingolimod (suspected/not suspected)
3. Duration (start and end dates or if continuing)
4. Whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- is fatal or life-threatening,
- results in persistent or significant disability/incapacity,
- constitutes a congenital anomaly/birth defect,
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication which is not associated with any deterioration in condition.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of registry participation.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition, or
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 4.2**

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); fingolimod dosage adjusted/temporarily interrupted; fingolimod permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made of any changes in severity, the suspected relationship to fingolimod, the interventions required to treat the adverse event, and the outcome.

Information about common side effects already known about fingolimod can be found in the most updated local product label. This information should be discussed with the patient as needed during the informed consent process.

[redacted]

## 4.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped registry participation must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported according to the reporter's normal practices for post-marketed adverse event reporting.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to fingolimod, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department. The telephone and telecopy number of the contact persons in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same department to which the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from registry participation.

If the SAE is not previously documented in the Package Insert (new occurrence) and is thought to be related to fingolimod, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting.

## 4.3 Pregnancies

In some countries (e.g European Union, Japan, Russia, Switzerland), fingolimod is contraindicated in the use relating to pregnancy. Latest local fingolimod product information and educational material for these countries should be referred to for guidance and more information.

To ensure patient safety, each pregnancy in a patient exposed to fingolimod must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

If physicians are aware of any pregnant patient they should try to enroll the patient and contact the CRO. If the physician's site is already set up and the patient has given written informed consent, data for this new patient can be directly entered into the registry database.

[redacted]

If the CRO becomes aware of a pregnancy they will report the pregnancy to Novartis within 24 hours. When the patient is enrolled in the registry follow up is done through the CRO and the local Novartis safety desk is informed by the CRO about any updates on the case.

If maternal exposed pregnancy information is reported to Novartis 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, Novartis 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 Novartis' Drug Safety & Epidemiology department should forward the reporter contact information to the CRO registry staff only if and after the reporter has provided their verbal consent, in accordance with local law and regulations.

### Pregnancy and SAE reconciliation

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

# 5 Statistical analysis

## 5.1 Statistical methods

Descriptive statistics will be used to summarize the findings; specifically, overall frequency (proportion, 95% confidence interval) of major malformations will be calculated, as well as frequencies of specific outcomes, e.g., heart defect, spina bifida, club foot deformity, cleft palate. The same will be calculated for minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, and any other adverse pregnancy outcomes. Minor anomalies will be grouped and reported as "defects case", if three or more occur in the same child. All primary analyses will be restricted to prospectively identified cases with outcome information available. Retrospectively identified cases (refer to Section 3.1 for description) will be collected and analyzed; however, these cases will not be included in any outcome rates calculated for the primary analysis. Multiple and singleton gestations will be presented separately.

The frequency of major malformations in the proposed registry will be compared to the frequency of major malformations in infants in the external comparison groups, i.e., MACDP (CDC) for US data, EUROCAT for European cases and data collected by external investigators including data made available from other registries that include pregnancy exposure and outcome information. Furthermore, using an internal comparison approach (if enough data is available), the risk of congenital anomalies among women with first trimester exposure will be compared with risks of congenital anomalies among women with second and third trimester exposure to investigate if there is an increased risk (risk estimate, 95% confidence interval) of major malformations among infants exposed to fingolimod.

In order to assess the overall generalizability and representativeness of the data included in this registry demographics of the registry population and the population of all pregnancy cases reported to pharmacovigilance will be summarized.

[redacted]

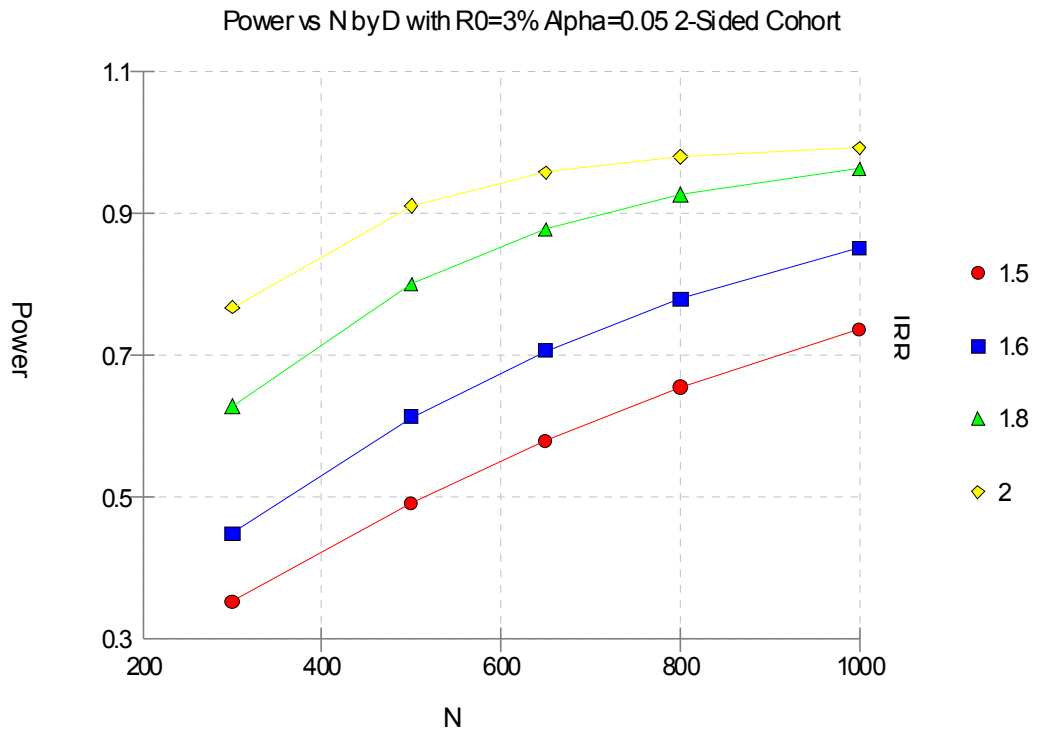
## 5.2 Sample size determination

In the US 3,030 infants with birth defects per 100,000 live births were reported by CDC (2010). The European surveillance of congenital anomalies (EUROCAT) reported a prevalence rate of 2334.2 per 100,000 live births (EUROCAT 2010). Worldwide about 6% of all newborn infants have serious birth defects of genetic or partially genetic origin and the annual prevalence of congenital malformations was 3,650 per 100,000 births (Christianson et al 2006).

The following chart (Figure 5-1) shows the power of this registry based on different numbers of women included to detect at least a 50% to 100% increased risk of any major malformation. Based on this assumptions the study will have >80% power (two-sided test, $\alpha$ set at 0.05) to detect a 80% risk increase if 500 women are included assuming a background prevalence of major malformations of 3% (nQuery Advisor 5.0).

Although it is expected that up to 500 women may potentially be enrolled during the at least four year recruitment period of the study, the rate of enrollment will not be known until actual accrual of patients begins (for details for the reasons for discontinuing this pregnancy registry refer to Section 3).

**Figure 5-1 Power based on number of included women (N) to detect a 50% to 100% risk increase based on a background prevalence of 3%**




[redacted]

## 5.3 Classification of exposures and outcomes

Although designed primarily as a prospective registry, the registry will accept retrospective reports of pregnancy outcome, meaning cases initially reported to the registry after the outcome is known. Similar to passive spontaneous case reporting, these reports may contribute to the differential reporting of poor outcomes but may also provide important information. The registry will allow for retrospective reports to be differentiated from prospective reports and analysis will be done separately. Although these cases do not contribute to the evaluation of true event rates in the exposed population, these cases may still provide important information.

Prenatal exposure will be summarized by trimester(s) exposed as well as exposure up to 8 weeks before LMP, dose and regimen. Exposures at specific gestational ages (in weeks) will be evaluated for individual cases. Exposure to other drugs and biologics will be collected, and HCPs will be able to indicate if there is a suspected, probable or known cause for any adverse pregnancy outcome. Trimesters will be defined as < 14 weeks (1st trimester), 14 to 27 weeks (2nd trimester) and ≥ 28 weeks (3rd trimester).

Spontaneous pregnancy loss will be defined as pregnancy loss at < 20 weeks gestation. Gestational age corrected by ultrasound will be used for gestational age when available, otherwise gestational age based on LMP will be used. Stillbirth (fetal death) will be defined as any pregnancy loss at ≥ 20 weeks gestation.

Low birth weight (LBW) is defined as < 2500 grams (5 pounds, 8 ounces) at birth and very low birth weight (VLBW) is defined as < 1500 grams (3 pounds, 4 ounces). Intrauterine growth retardation (IUGR) will be defined as estimated fetal weight below the 10th percentile for gestational age. It is important to note, however, that as many as 70% of fetuses who are estimated to weigh below the 10th percentile for gestational age are small simply due to constitutional factors such as female sex or maternal ethnicity, parity, or body mass index (Manning 1995). This definition covers all small for gestation fetuses and does not make a distinction among fetuses who are constitutionally small, growth restricted and small, and growth restricted but not small; therefore, any report of IUGR in the exposed population will require further assessment to ensure the case is appropriately categorized. In addition, cases where the physician has reported decreased relative growth even though the infant is > 10th percentile, may be included in the overall analysis of potential in-utero growth restriction. Moderate and severe IUGR will be defined as fetal weight in the 3rd to 10th percentile and less than 3rd percentile, respectively (Peleg et al 1998). For infants, the same criteria (i.e., weight below the 10th percentile for gestational age) will be applied but referenced as small for gestational age (SGA) at birth. An infant who is larger than expected for the age and gender, with a birth weight above the 90th percentile, will be considered large for gestational age (LGA).

Structural and functional congenital anomalies identified in the perinatal period through one year of age will be collected and classified. The registry will utilize congenital anomaly definitions and classifications consistent with the MACDP and the EUROCAT surveillance programs (i.e., ICD9 or ICD10-BPA), to the extent possible, in order to facilitate comparisons (details regarding coding and classification, and case definition, will be established in registry-specific clinical review procedures). Both coding methods will be utilized.

[redacted]

Chromosomal abnormalities (and genetic disorders) will be evaluated separately due to the low likelihood that these defects would be associated with drug exposure. Defects identified outside of the study period may also be reported to the registry, but it is not the intention of the registry to pursue long-term data (> one year) regarding the offspring. All congenital anomalies reported will be reviewed periodically by a clinical reviewer who will determine whether additional follow-up with the reporting physician is required in order to classify the event (including classification into minor or major anomalies), and will review the coded datasets overall for accuracy and internal consistency. The calculation for risk of congenital malformations will be made by dividing the number of congenital anomalies associated with any pregnancy outcome by the sum of the number of live births without congenital anomalies and any outcomes involving congenital anomalies. Estimates of risk will also be analyzed as stratified by trimester of exposure.

# 6 Registry operations

All registry operations, including development of materials, training and management of sites, quality control of data collection and data management will be performed by the CRO according to their SOPs with guidance, input, review and approval by Novartis.

## 6.1 Registry enrollment

### 6.1.1 Type of registry sites

Two different types of sites will be targeted for recruitment:

- National Coordinating Site (NCS): Acts as Principal Investigator with IRB/EC/HA approvals and contract. Will enroll and follow-up patients at their own site, and coordinate enrollment at Sentinel Sites. In the US and Canada the CRO will act as a NCS.
- Sentinel Site (SS): Will be recognized as such and set up only after they have an eligible patient. Depending on the decision of the investigator a SS can act as a Co-Investigator of the NCS or they can be set up as independent Principal Investigators.

### 6.1.2 Patient enrollment

Patients may be enrolled by the NCS or a Sentinel site. NCS will already be set up as a site. Sentinel sites will choose their preferred method for contacting the registry. Options will include:

- Dedicated toll-free number: the phone call will be performed in local language by qualified personnel. All personnel will be trained on the registry procedures as appropriate. A standard script will be used to collect patient contact information (only US and Canada) as well as HCP information.
- Paper form: the investigator will have the ability to print a contact form to be completed and mailed or faxed to the CRO.
- Online form: an electronic contact form will be available on the registry website portal.

After the first contact with the registry team the HCP will be provided with the Gilenya Pregnancy Registry start-up package and all the required training on the registry as appropriate.

[redacted]

### 6.1.3 Patient self-registration in the US and Canada

In the US and Canada a patient can initiate her self-registration as follows:

- Patients can call the dedicated registry toll-free telephone number to self-register. The phone call will be performed in local language by qualified personnel. All personnel will be trained on the registry procedures as appropriate. A standard script will be used to collect patient contact information as well as HCP information if the patients have provided their verbal consent. Patients will provide their contact details and that of their HCP(s) in order for the CRO to contact the HCP(s) who will be asked if he/she is able to participate. If he/she agrees, the CRO will send him/her the Gilenya Pregnancy Registry start-up package including the username and password for the EDC system.
- Patients can also self-register via the registry website. They will provide their contact details and that of their HCP(s) in order for the CRO to contact the physician.

In countries where patient self-registration is not possible: If patients contact the CRO directly, they will be asked to contact their HCP(s) and ask him/her to contact the CRO. If the HCP is not able to participate in the registry, he/she will be asked to refer his/her patient to the NCS or another HCP who is able to participate.

## 6.2 Data collection and data entry

Data collected at any of the National Coordinating Sites will be entered by the NCS staff directly into the EDC system via eCRFs. All NCS will be fully trained for using the on-line data capture system, including eCRF completion guidelines. It is the registry physician's responsibility to ensure the accuracy of the data provided to the registry and that any NCS staff is trained for registry data collection. Where technical conditions prevent the entry by using eCRFs, paper CRFs may be used and sent to the CRO for entry into the EDC system.

Different methods for providing data to the registry will include:

1. Completing eCRFs online through a link that will grant access to the EDC system registry database.
2. Completing paper CRFs and returning them to the CRO by postal mail using prepaid envelopes for entry into the EDC system by the CRO staff.
3. Completing CRF on the phone via outbound call from the CRO call centre. The phone call will be performed in local language by qualified personnel. All personnel will be trained on the registry procedures as appropriate. A standard script will be used to collect information for entry into the EDC system by the CRO staff.
4. Medical record abstraction and data entry by the CRO: In rare circumstances, the CRO staff may visit a participating site (NCS or SS) to review patient medical records in order to complete the eCRFs. This will only be done if none of the methods mentioned above are possible.

In the event that none of the data collection options described in this section are feasible, the CRO registry staff may collect the data from the patient directly, if acceptable by law. Patient self-reported data can be collected over the phone by the CRO. The data collected over the phone will be entered in the registry database by the CRO staff.

[redacted]

The registry is purely observational and does not entail any change in prescribing pattern or management policies which are left to the discretion of the treating physician. No special evaluation procedure is required. The data to be entered in the CRF is part of the information that should be generally available during good medical care.

On a regular basis, when analysis is planned and after quality assurance procedures have been completed, the database will be frozen and a dataset created so that no further changes take place and analysis can be implemented. Data will be transferred to Novartis after closure of the registry.

## 6.3 Data management and monitoring

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

In order to ensure the integrity of the data, a clinical research associate (CRA) may visit the physician's office at periodic intervals to review registry records and source documentation according to the monitoring plan, as well as to discuss the conduct of the registry. The CRA may require access to all registry documents. Registry monitoring reports will be kept strictly confidential.

During the site initiation visit, the CRA will provide training on the conduct of the registry to the participating physician and all site staff involved in the registry. The CRA will close-out each site after the last patient's final follow-up visit has been completed, all data have been received and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures and the frequency of monitoring visits (both scheduled and for-cause) will be described in a monitoring plan.

## 6.4 Study governance

The registry will be conducted by the CRO with the guidance, support and oversight of the Novartis project team and an independent Advisory/Steering Committee.

The registry's independent Advisory/Steering Committee, consisting of relevant experts (e.g., epidemiologists/statisticians, neurologists, perinatologists, pediatricians and/or neonatologists) will oversee the progress of the registry, provide recommendations on changes to the registry, review annual reports and advise on any identified potential safety signals, as needed. The composition, duties and responsibilities of the committee, including meeting frequency, will be detailed in a committee charter.

In general, the roles of the Advisory/Steering Committee are to:

- Advise Novartis on the design, implementation and scientific conduct of the pregnancy exposure registry study
- Ensure the scientific integrity of the registry and help to maximize enrollment of eligible patients to receive data for evaluation with good scientific internal and external validity

[redacted]

- Make recommendations for analysis plan and how the data outputs should look like
- Review additional data as required for interpretation of registry findings
- Potentially communicate with other MS registries regarding potential synergies and data-sharing

All considerations regarding publication rights are detailed in Section 8.3.

# 7 Ethical and regulatory considerations

## 7.1 Regulatory and ethical compliance

To ensure the quality and integrity of research, this study will be conducted under the *Guidelines for Good Pharmacoepidemiology Practices* issued by the International Society for Pharmacoepidemiology (ISPE), the principles outlined in the Declaration of Helsinki, and any applicable national guidelines.

All data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Patients must be informed accordingly, and will be asked to give their consent on data-handling procedures in accordance with national regulations in place in each of the countries included in the study. The data will be collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes. In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier created randomly upon registry enrollment. This patient identifier will be used in place of patient name for the purpose of data analysis and reporting. Medical record number or other local reference identifiers are not collected as part of the database. The protected health information critical to the registry are milestone dates from which the mother could potentially be identified, such as date of last menstrual period, expected date of delivery and dates of treatment exposure. Patient contact information will not be included in any registry reports.

## 7.2 Responsibilities of the treating physician and IRB/IEC

The protocol and the proposed informed consent form will be reviewed and approved by a properly constituted institutional review board (IRB) or independent ethics committee (IEC) before study initiation, or alternatively IRB/IEC notification will be provided, as appropriate. Prior to study start, the participating physician will be asked to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with the protocol and to give access to all relevant data and records to Novartis and their representatives, IRBs/IECs, and regulatory authorities, as required. Should the study be terminated early for any unanticipated reason, the treating physician will be responsible for informing the IRB/IEC of the early termination.

Changes to the protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the relevant IRB/IECs for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained. Minor (non-substantial) protocol amendments, including administrative changes, will be filed by Novartis

[redacted]

and/or the CRO and at each participating site (NCS and SS). They will be submitted to the relevant IRB/IEC where required by pertinent regulations. Any amendment that could have an impact on the subject's agreement to participate in the study, e.g., changing the nature of the data collected, requires the patient's informed consent prior to implementation.

## 7.3 Informed consent procedures

Eligible patients enrolling in the study may only be included in the study after providing written (witnessed, where required by law or regulation) informed consent on an IRB/IEC approved informed consent form, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. Patients will be consented by their HCPs either in person or remotely over the phone by a NCS using an IRB/IEC approved phone script where required by law and local regulations. The consent process will be documented in writing and a copy of the signed informed consent form will be filed in the investigator site file.

For the purposes of follow-up with the infant's pediatrician, the patient will be expected to provide proxy informed consent on behalf of the infant. Where possible, this proxy consent will be included in the patient's informed consent signed at enrollment. Otherwise, prior to the collection and entry of post-partum and one year follow-up data, the HCP will be required to obtain informed consent from the patient on behalf of the infant (where required, consent of both parents will be sought). Registry staff from the CRO will provide reminders to HCPs at appropriate time points to ensure the consent is obtained.

Informed consent forms will be provided in the local language(s) of each country. In cases where the patient's representative gives consent, the patient should be informed about the registry to the extent possible given his/her understanding. Informed consent must be obtained before conducting any registry-related data collection. The process of obtaining informed consent should be documented in the patient source documents.

Sites will be provided with an informed consent form template that complies with the relevant guidelines and regulatory requirements. Any changes to the proposed consent form suggested by the site must be agreed to by Novartis before submission to the IRB/IEC for approval and a copy of the approved version must be provided to Novartis after IRB/IEC approval.

# 8 Recordkeeping, data reporting, data quality assurance and publications

## 8.1 Source document retention and archiving

The site is expected to maintain a record of each patient enrolled in the registry. Physician evaluations recorded directly into the eCRF will be considered as source data. Registry physicians will be instructed on source documentation that must be available to substantiate patient identification, eligibility and participation, proper informed consent procedures, dates of data collections, adequate reporting and follow-up of adverse events, concomitant medication and exposure to fingolimod. In addition, all original source documentation, including patient-completed forms and medical records, is expected to be stored at the site for the longest possible time, as defined and required by local applicable regulations. Each

[redacted]

registry site will receive a site file upon initiation of the registry containing all documents necessary for the conduct of the registry which will be updated throughout the registry. The site file must be available for review in the event the site is selected for monitoring, audits, or inspections.

## 8.2 Data quality assurance

The registry database will be housed at the offices of the CRO in a physically and logically secure computer system maintained by the CRO in accordance with the CRO's written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of the International Council for Harmonisation (ICH) guideline E6R1 and 21CFR§11 regarding electronic registry data handling, and is available for audit upon request. Patient confidentiality will be strictly maintained.

## 8.3 Publication of results

Upon registry completion and finalization of the registry report, the results of the registry may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

If the Institution / Investigator wishes to make any publication or presentation relating to the pregnancy registry, at meetings or otherwise, the Institution / Investigator shall provide to CRO and Sponsor any proposed presentation at least 15 (fifteen) working days prior to being disclosed and any other proposed publication at least 45 (forty-five) working days prior to being disclosed, and provided that Sponsor through CRO or its designee shall have the right to require amendments to any such proposed presentation or publication on reasonable grounds including without limitation:

- To ensure the accuracy of the presentation or publication;
- To ensure that proprietary information is not inadvertently divulged;
- To enable intellectual property rights to be secured;
- To enable relevant supplementary information to be provided.

The Institution / Investigator shall be required to comply with any request to amend or delete any statement in a proposed publication, provided such request is based on any one of (a) to (d) above.

The CRO or Sponsor may require any proposed publication or presentation to be delayed for up to 4 (four) months to enable a patent application to be prepared and filed. The 4 (four) month period shall commence on the date of receipt of the proposed publication or presentation, or from the date when all relevant data from the pregnancy registry are made available to Sponsor, whichever is later. As this is a multi-centre registry, the first publication of data shall be based on consolidated data from all centers analyzed according to the Protocol, unless otherwise agreed in writing by all the Principal Investigators involved in the registry and by the Sponsor.

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A publication plan will document additional priorities and authorship of abstracts and publications in accordance with applicable Novartis internal policies and standards.

# 9 Strengths and limitations

A major strength with the proposed pregnancy exposure registry is that data are being collected prospectively, that is, a woman is enrolled after the fetus has been exposed but before the outcome of the pregnancy is known, and is then followed to the end of the pregnancy. Typically with spontaneous adverse event reports the infant is already born and the likelihood of reporting including the assessment of past exposures might be biased by an adverse outcome. Limitations with spontaneous adverse event reports include lack of denominator data, absence of controls, recall and selection bias due to retrospective reporting, and poor case documentation.

Interpretation of the data collected is somewhat limited by the use of external controls to evaluate the findings of this registry; however, the possibility of including diseased patients not exposed to any compound is very limited and the resulting power of such a comparison group very low and most often not leading to informative results. In contrast, a large comparison population from the general population can be considered a more conservative approach and allows the detection of a possible signal earlier. In addition, there is currently no evidence to suggest that the rate of major congenital anomalies in patients with underlying multiple sclerosis is different than the general population. In addition, case series and prospective studies, although mostly small in size, exist in the literature that should serve as additional context for both malformations and other adverse fetal and pregnancy outcomes.

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