PROTOCOL TITLE:	Biogen Multiple Sclerosis Pregnancy Exposure Registry
VERSION:	Version 5 (European Union)
DATE:	29 March 2016
EU PAS REGISTER NUMBER:	ENCEPP/SDPP/3976
ACTIVE SUBSTANCE:	N07XX09 Dimethyl fumarate (DMF) and Daclizumab high yield process (DAC HYP)
MEDICINAL PRODUCT:	Tecfidera® 120- and 240-mg gastroresistant hard capsules and Zinbryta™ 150 mg subcutaneous injection
PRODUCT REFERENCE:	EU/1/13/837
PROCEDURE NUMBER:	EMEA/H/C/2601
MARKETING AUTHORISATION HOLDER:	Biogen MA Inc. and Biogen Idec Research Limited
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES	The purpose of this study is to better characterize how a marketed Biogen multiple sclerosis (MS) product specified in this Pregnancy Registry (DMF or DAC HYP), henceforth known as a "Registry-specified Biogen MS product," may affect pregnancy and infant outcomes. The primary objective of the study is to prospectively evaluate pregnancy outcomes in women with MS who were exposed to a Registry-specified Biogen MS product during the eligibility window for that product.
COUNTRIES OF THE STUDY:	Global study including countries in North America, Australia, and the European Union.
AUTHOR:	[redacted], PhD [redacted] Biogen MA Inc. Tel.: [redacted]

This version supersedes Version 4 dated 30 September 2015.

MARKETING AUTHORISATION HOLDER INFORMATION

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31 MAR 2016
Date

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30/MARCH/2016

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Date

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Biogen Idec Research Limited

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2. LIST OF ABBREVIATIONS

AE	adverse event
BID	twice daily
CC	Coordinating Center
CI	confidence interval
CRF	case report form
CRO	contract research organization
DAC HYP	daclizumab high yield process
DMF	dimethyl fumarate
EDD	estimated date of delivery
EMA	European Medicines Agency
ENCePP	The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUROCAT	European Surveillance of Congenital Anomalies
FDA	Food and Drug Administration
GD	gestational day
HCP	health care provider
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ICF	informed consent form
Ig	immunoglobulin
LMP	last menstrual period
MRI	magnetic resonance imaging
MS	multiple sclerosis
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
US	United States

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Table 1: Abstract for Protocol 109MS402

Protocol Title:	Biogen Multiple Sclerosis Pregnancy Exposure Registry
Version Number:	5 (European Union)
Date of Protocol:	29 March 2016
Name and Affiliation of Main Author:	[redacted], PhD [redacted] Biogen MA Inc.
Rationale and Background:	Women of childbearing potential are a considerable segment of the patient population affected by multiple sclerosis (MS) and are likely to be exposed to a marketed Biogen MS product specified in this Pregnancy Registry (dimethyl fumarate [DMF] and daclizumab high yield process [DAC HYP]), henceforth known as a "Registry-specified Biogen MS product," around the time of conception and during pregnancy. Biogen completed pregnancy registries for Avonex® and Tysabri®; however, registries for several other MS products have not been completed. Therefore, it is important to evaluate, in a global Pregnancy Registry, how exposure to a Registry-specified Biogen MS product may affect pregnancy and infant outcomes.

Research Question and Objectives:	The purpose of this Pregnancy Registry is to better characterize how a Registry-specified Biogen MS product may affect pregnancy and infant outcomes. *Objectives* The primary objective of the study is to prospectively evaluate pregnancy outcomes in women with MS who were exposed to a Registry-specified Biogen MS product during the eligibility window for that product. • DMF: Exposure since the first day of her last menstrual period (LMP) prior to conception or at any time during pregnancy • DAC HYP: Exposure since 90 days prior to the first day of her LMP prior to conception or at any time during pregnancy **Pregnancy Outcome Classification** The outcome measures in Registry-specified Biogen MS product-exposed pregnant women and their offspring include • pregnancy loss (elective or therapeutic pregnancy terminations, spontaneous abortions, and fetal death, including stillbirths) • live birth (premature birth and full-term birth) Ectopic pregnancies, molar pregnancies, and birth defects or congenital anomalies (including minor anomalies) that occur up to 52 weeks of age of the offspring will be reported for each pregnancy outcome. The occurrence of any infant death occurring up to 52 weeks of age will also be reported. In addition, maternal deaths that occur up to 12 weeks postdelivery will be reported.

Study Design:	This is a prospective, observational registry in pregnant women with MS who were exposed to a Registry-specified Biogen MS product during the eligibility window for that product. After a patient provides consent, the Coordinating Center (CC) Investigator will obtain demographic and contact information in addition to baseline medical history at the time of enrollment (Note: The contact information will be confidential and remain at the CC). Thereafter the CC will contact the patient once per trimester to update contact information and ascertain the occurrence of a pregnancy outcome. The CC will contact the patient's obstetric and neurologist health care provider (HCP) at 6 to 7 months of gestation for the Prenatal Follow-Up and at approximately 4 weeks after the estimated date of delivery for the Pregnancy Outcome Follow-Up. At approximately 4, 12, and 52 weeks after birth, the CC will contact the pediatric HCP for a Pediatric Follow-Up.
Population:	This study will be conducted in pregnant women with MS who were exposed to a Registry-specified Biogen MS product during the eligibility window for that product.
Variables:	Refer to Study Design, above
Data Sources:	The CC will collect the Registry data from patients with MS who become pregnant while being treated with a Registry-specified Biogen MS product and from their HCPs.

Study Size:	Within each product cohort, it is anticipated that approximately 310 to 375 pregnant women exposed to a Registry-specified Biogen MS product will be enrolled in order to observe 300 prospective pregnancy outcomes. Patients with prenatal testing prior to enrollment (with the exception of a first trimester ultrasound to date the pregnancy) and their pregnancy outcomes will not be counted towards the 300 prospective pregnancy outcomes. Based upon 300 observed prospective outcomes and on a 2-sided exact test for a single proportion with $\alpha = 0.05$, the study will have at least 80% power to detect prevalence rate ratios of 2.9 for birth defects and 1.52 for spontaneous abortions.

Data Analysis:	Analyses will be conducted separately for each cohort. The prevalence of birth defects and spontaneous abortions and 95% confidence intervals (CIs) for the Registry population will be calculated to assess the presence or absence of any excessive risk associated with exposure to a Registry-specified Biogen MS product. All analyses will be conducted on an overall basis, as well as stratified by earliest trimester exposure. Other negative pregnancy outcomes will be similarly examined as the sample size in each cohort permits. As appropriate and where sample size permits, birth defect reporting rates and spontaneous abortion rates from the Registry will be compared with their respective rates from published reports of commercially available MS therapies from other ongoing registries. Additional comparisons of the reporting rates from each cohort within the Registry will be conducted against available background rates from various sources such as the European Surveillance of Congenital Anomalies (commonly known as EUROCAT), the International Clearinghouse for Birth Defects Surveillance and Research (commonly known as ICBDSR) System, and/or the March of Dimes, as appropriate. Within each cohort, comparative analyses of Registry reports will include only prospective reports (i.e., reports received before knowledge of the pregnancy outcome is known; patients who underwent informative prenatal testing are permitted to participate in the Registry). These comparisons will be based on examination of point estimates of event rates and 95% CIs. Inclusion of patients with prenatal testing may introduce bias into the study. Therefore, some analyses may be stratified by prenatal testing status at enrollment. The denominator for calculating reporting rates of negative pregnancy outcomes will include only prospective reports (where prospective registration is defined as a report of a Registry-specified Biogen MS product-exposed pregnancy enrolled before the outcome of the pregnancy is known). Each Registry-specified Biogen MS product will have its own statistical analysis plan.

5. AMENDMENTS AND UPDATES

Substantial amendments and updates to this protocol since the beginning of data collection are listed in Table 2.

Table 2: Substantial Amendments and Updates to Protocol 109MS402

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	30 September 2015	Section 9	4	To include patients who have had diagnostic prenatal testing prior to enrollment and to stratify patients based on their prenatal testing status to limit bias and allow for a more robust assessment of birth defect risk. The sample size was increased to accommodate this change.
2	30 September 2015	Section 9	4	To remove the Metropolitan Atlanta Congenital Defects Program (MACDP) as an external registry comparator because the MACDP population differs from that of the Registry.
3	29 March 2016	Sections 2, 7, 8, 9, 11, 13, and16	5	To add a second Biogen MS Product, DAC HYP, to the Pregnancy Registry to allow for better synergies between study sites, personnel, and other sources, and better harmonization between product databases.
4	29 March 2016	Sections 9 and 13	5	To update estimated prevalence rate ratios that the study has 80% power to detect based on more recent data for birth defects and spontaneous abortions.

DAC HYP=daclizumab high yield process

6. MILESTONES

Milestone dates are communicated outside of the protocol.

7. RATIONALE AND BACKGROUND

Biogen has elected to conduct a single Pregnancy Registry with individual product cohorts. A brief description of each product included in this registry is listed below.

Tecfidera

Tecfidera® is an oral treatment for relapsing multiple sclerosis (MS). Tecfidera is a fumarate ester drug product containing the active ingredient dimethyl fumarate (DMF), which in the body is rapidly and almost completely converted to its primary metabolite, monomethyl fumarate, also an active agent.

The efficacy of DMF has been demonstrated during clinical development in 2 large pivotal Phase 3 studies (109MS301 and 109MS302) in subjects with relapsing remitting MS. Both doses of DMF investigated (240 mg twice daily [BID] and 3 times daily) were effective in reducing measures of relapse, delaying the accumulation of disability associated with MS, and improving magnetic resonance imaging (MRI) measures of MS disease activity.

As of 26 March 2015, a total of 3887 MS subjects have received at least 1 dose of DMF in the clinical development program. Overall, the safety data from the clinical development program showed that DMF was well tolerated and has an acceptable safety profile.

Zinbryta

Zinbryta™ (daclizumab high yield process [DAC HYP]) is a monoclonal immunoglobulin (Ig) of the human IgG1 isotype that binds specifically to the alpha subunit (CD25) of the human high-affinity interleukin (IL)-2 receptor (IL-2R) that is expressed on the surface of activated lymphocytes [Waldmann 2007]. The antibody is expressed as a disulfide-linked tetramer of 2 heavy and 2 light chains. The heavy chain is human gamma-1 and the light chain is human kappa [Queen 1989].

The efficacy of DAC HYP for the treatment of relapsing remitting MS has been evaluated in 2 pivotal studies (205MS201 [Phase 2] and 205MS301 [Phase 3]). The 150 mg dose was effective in reducing measures of relapse and improving MRI measures of MS disease activity compared with both placebo and interferon β-1a and, additionally, in delaying the accumulation of disability associated with MS compared with placebo. As of 07 January 2015, 127 healthy volunteers and 2236 subjects with MS have received DAC HYP in clinical studies. The most important identified risk observed in clinical studies was an increased number of cases of hepatic injury and incidence of transaminase elevations; 4 other important identified risks were cutaneous events, depression, infections, and colitis. Overall, the adverse events (AEs) were able to be monitored through laboratory testing and routine history and physical examinations. With the exception of 1 case of death due to autoimmune hepatitis, the events were generally self-limited and improved after suspending or stopping therapy with DAC HYP, or they were manageable with standard-of-care therapies.

7.1. Profile of Previous Experience

7.1.1. Nonclinical Reproductive Toxicology Experience

7.1.1.1. Nonclinical Reproductive Toxicology Experience With DMF

DMF was evaluated in animal reproductive studies. No DMF-related fertility effects were observed in male and female rats at oral doses up to 375 mg/kg/day and up to 250 mg/kg/day, respectively (9 and 6 times the BG00012 240 mg BID dose in humans, respectively, on a mg/m^2 basis). In embryofetal developmental studies, no DMF-related malformations were observed in rats and rabbits at maternally toxic oral doses up to 250 mg/kg/day and up to 150 mg/kg/day, respectively. Reductions in fetal weight and fetal variation of delayed ossification in metatarsals and hindlimb phalanges in rats (6 times the BG00012 240 mg BID dose in humans on a mg/m^2 basis) and increased abortion in rabbits (7 times the BG00012 240 mg BID dose in humans on a mg/m^2 basis) were attributed to maternal toxicity. In the pre- and postnatal developmental study in rats, the no-observed-adverse-effect level for viability and growth in the offspring was DMF 100 mg/kg/day. At DMF 250 mg/kg/day, reduction in pup body weights and delayed sexual maturity in male rats (6 times the BG00012 240 mg BID dose in humans on a mg/m^2 basis) were attributed secondarily to the overt maternal toxicity.

7.1.1.2. Nonclinical Reproductive Toxicology Experience With DAC HYP

The reproductive and developmental toxicity for DAC HYP has been thoroughly evaluated. DAC HYP had no effects on male or female fertility as assessed by surrogate markers of fertility (hormones, sperm count, sperm motility or morphology, menstrual cycle, and ovarian function [serum estradiol and progesterone]) at doses up to 200 mg/kg (highest dose tested). DAC HYP had no effects on fetal development in the developmental and reproductive toxicity study where it was administered subcutaneously within 2 days of confirmed pregnancy (approximately on gestational day [GD]20) and weekly thereafter until GD50 at doses up to 200 mg/kg (highest dose tested). The 200-mg/kg dose corresponds to an exposure that is 140-fold the human exposure at the 150-mg efficacious dose.

There were no effects on pre- and postnatal development as evaluated in pregnant cynomolgus monkeys where DAC HYP (50 mg/kg) was administered subcutaneously to pregnant monkeys once weekly from GD50 until parturition (approximately GD160 ± 10). This dose provides a 55-fold safety margin over the recommended therapeutic dose. This study included evaluation of growth and development of offspring for up to 6 months postnatally. There were no DAC HYP-related effects observed on pregnancy or postpartum outcomes, or on any developmental parameters for the offspring including neurobehavioral effects, or immunomodulatory effects on peripheral blood lymphocytes as assessed by immunophenotyping or the ability to mount a T-cell dependent humoral response, nor were there any microscopic findings in the brains of the offspring.

7.1.2. Clinical Experience in Pregnant Women

7.1.2.1. Clinical Experience With DMF in Pregnant Women

No formal studies of DMF in pregnant women have been performed.

As of March 2015, 529 cases with a total of 590 events (311 from clinical studies and 279 consumer-reported events) involving patients with exposure to BG00012 during pregnancy (including 22 reports of paternal exposure) were received.

During the clinical studies, 106 pregnancies were reported as of March 2015 in female subjects treated with BG00012. The outcome is available for 68 pregnancies; 42 (62%) resulted in live births, 18 (27%) were terminated electively, and 8 (12%) were spontaneously aborted. Six of the 36 live births were premature births at <37 weeks of gestation. Of the elective terminations, there were 2 reports of fetal abnormalities in the BG00012-treated group. The rate of spontaneous abortions, including early pregnancy losses, does not exceed the expected rate of the general population of approximately 15% to 20% [Garcia-Enguidanos 2002].

Based on the current data, there is no evidence of increased risk of fetal abnormalities or adverse pregnancy outcomes associated with gestational exposure to DMF during the first trimester. However, because there are no adequate and well-controlled studies in pregnant women and because animal studies are not always predictive of human response, it is recommended that DMF should only be used during pregnancy if there is a clear need for MS treatment and if the potential benefit justifies the potential risk to the fetus.

7.1.2.2. Clinical Experience With DAC HYP in Pregnant Women

There are no data on the effects of DAC HYP on human fertility.

There are limited data on the use of DAC HYP in pregnant women. DAC HYP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Refer to the study protocols for specific information on contraception requirements. Refer to and follow the specific guidelines regarding use of DAC HYP in pregnant women as specified in the clinical study protocols.

Labor and Delivery

The effects of DAC HYP on labor and delivery are unknown.

Women of Childbearing Potential

The benefit of treatment with DAC HYP versus potential risk should be discussed with women of childbearing age or women who become pregnant during therapy.

7.2. Registry Rationale

MS is an immune-mediated, demyelinating disorder of the central nervous system. Prevalence in the United States (US) and Europe varies from 250,000 to 300,000 [Coyle 2004]. Two thirds of patients with MS are women, and approximately 10% have disease onset during pregnancy [Bennett 2005]. As such, women of childbearing potential are a considerable segment of the patient population affected by MS and are likely to be exposed to a marketed Biogen MS product

specified in this Pregnancy Registry (DMF or DAC HYP), henceforth known as a "Registry-specified Biogen MS product," around the time of conception and during pregnancy. Biogen completed pregnancy registries for Avonex® and Tysabri®; however, registries for several other MS products have not been completed. Therefore, it is important to evaluate, in a global Pregnancy Registry, how exposure to a Registry-specified Biogen MS product may affect pregnancy and infant outcomes.

8. RESEARCH QUESTION AND OBJECTIVES

The purpose of this study is to better characterize how a Registry-specified Biogen MS product may affect pregnancy and infant outcomes.

8.1. Primary Objective

The primary objective of the study is to prospectively evaluate pregnancy outcomes in women with MS who were exposed to a Registry-specified Biogen MS product during the eligibility window for that product. The Registry-specified Biogen MS products included in this Pregnancy Registry are described in Section 7. The eligibility window for each included product is defined in Section 9.2.1.2.

The primary outcomes are described in Section 9.1.1 and further defined in Section 9.3.1.

9. RESEARCH METHODS

9.1. Registry Design

This is a prospective, observational registry designed to evaluate pregnancy outcomes in women with MS who were exposed to a Registry-specified Biogen MS product during the eligibility window for that product. The primary outcomes are described in Section 9.1.1. The registry design is described in Section 9.2.1.

In an effort to ensure that the Pregnancy Exposure Registry collects, analyzes, and presents information that is accurate and useful to the health care providers (HCPs) and others, the Registry will conform to the European Medicines Agency (EMA) Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post Authorisation Data [EMA 2005] and the US Food and Drug Administration (FDA) Guidance for Industry [FDA 2002].

9.1.1. Pregnancy Outcomes

The Registry's definition of pregnancy losses and other adverse pregnancy outcomes is consistent with the European Surveillance of Congenital Anomalies (EUROCAT) and the EMA pregnancy guidance. Alternative definitions will be used as appropriate to compare data from the Centers for Disease Control and Prevention, the National Center for Health Statistics, the National Institute for Health and Welfare, and the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) System. All cases will be reviewed based on earliest exposure to a Registry-specified Biogen MS product.

Pregnancy outcomes will be classified as pregnancy loss or live birth, as defined below:

- Pregnancy loss
    - elective or therapeutic pregnancy terminations (any induced or voluntary fetal loss during pregnancy)
    - spontaneous abortions (<22 weeks of gestation)*
    - fetal death, including stillbirths (fetuses born dead at ≥22 weeks of gestation), which will be further classified as follows:
        - early fetal loss (fetal death occurring at ≥22 weeks but <28 weeks of gestation)*
        - late fetal loss (occurring at ≥28 weeks of gestation)

  *Pregnancy loss outcomes will also be classified using definitions consistent with the FDA pregnancy guidance [FDA 2002]: spontaneous abortions (<20 weeks of gestation) and early fetal loss (≥20 weeks of gestation).

- Live birth**
    - premature birth (delivered <37 weeks)
    - full-term birth (delivered ≥37 weeks)

**The occurrence of an infant death up to 52 weeks of age as defined in Section 9.3.1 will further be reported in all live births.

In addition, the occurrence of ectopic pregnancies, molar pregnancies, and birth defects or congenital anomalies (including minor anomalies) that occur up to 52 weeks of age of the offspring will be reported in each pregnancy outcome (refer to Section 9.3.1). All potential birth defects, including minor anomalies, will be adjudicated and grouped into appropriate categories by a qualified independent teratologist or other appropriate birth defect evaluator.

In addition, maternal death (death during pregnancy, labor, or delivery) will be reported. Maternal deaths occurring up to 12 weeks postdelivery will also be reported.

9.2. Setting

9.2.1. Registry Design

9.2.1.1. Registry Overview

HCPs who treat patients with MS, including Investigators in ongoing or future clinical studies of a Registry-specified Biogen MS product, will be informed of the Registry and asked to report any patient who becomes pregnant while being treated with a Registry-specified Biogen MS product. Reporting of pregnancy exposures to a Registry-specified Biogen MS product is voluntary. Pregnancies should be reported as early as possible, ideally before prenatal testing has been performed. Pregnancies with known outcomes (i.e., pregnancy loss or live birth) at the time of the initial report (i.e., retrospective cases) will not be included in the Registry but will be followed by Biogen Safety and Benefit-Risk Management (SABR) according to standard postmarketing pharmacovigilance practice.

After a patient provides consent, the Coordinating Center (CC) Investigator will obtain demographic and contact information in addition to baseline medical history at the time of enrollment (Note: The contact information will be confidential and remain at the CC). Thereafter the CC will contact the patient once per trimester to update contact information and ascertain the occurrence of a pregnancy outcome. The CC will contact the patient's obstetric and neurologist HCP at 6 to 7 months of gestation for the Prenatal Follow-Up and at approximately 4 weeks after the estimated date of delivery (EDD) for the Pregnancy Outcome Follow-Up. At approximately 4, 12, and 52 weeks after birth, the CC will contact the pediatric HCP for the Pediatric Follow-Up.

9.2.1.2. Selection Criteria for Prospectively Enrolled Pregnant Patients in the Registry

To be eligible to participate in this Registry, candidates must meet the following eligibility criteria prior to enrollment (i.e., eligibility is to be confirmed with the patient prior to the patient consenting to be enrolled in the Registry):

1. Patient consent (written or verbal per local regulations or ethics committee requirements) must be obtained prior to the patient's enrollment. If the patient is a minor, written consent must be obtained from their parent or legal guardian.
2. Patient has a diagnosis of MS.

3. Documentation that the patient was exposed to a Registry-specified Biogen MS product during the eligibility window for that product. (If exact exposure dates are unknown, the reporter must be able to specify or estimate trimester of exposure.)
    a. DMF: Exposure since the first day of her last menstrual period (LMP) prior to conception or at any time during pregnancy
    b. DAC HYP: Exposure since 90 days prior to the first day of her LMP prior to conception or at any time during pregnancy
4. Patient agrees to sign the Release of Medical Information Form, thereby permitting the Registry to contact her HCP(s) and the pediatric HCP for medical information.
5. Initial maternal health assessment upon confirmation of pregnancy does not preclude participation in the Registry unless a patient tests positive for a medical condition associated with negative pregnancy outcomes (e.g., toxoplasmosis screen and syphilis [venereal disease research laboratory test and rapid plasma reagin test] blood screen) in the opinion of the HCP.
6. The outcome of the pregnancy (i.e., pregnancy loss or live birth) must not be known at the time of enrollment.

Pregnant patients may be enrolled prospectively from:

- the postmarketing setting
- observational studies for an approved Biogen MS product (e.g., 109MS401)
- other clinical studies for a Registry-specified Biogen MS product (patients may be dually enrolled in a clinical study and in the Registry)

For pregnancies with outcomes that are known (i.e., pregnancy loss or live birth) at the time of the initial report (i.e., retrospective cases), the information will be collected outside of this Registry by Biogen SABR according to standard postmarketing pharmacovigilance practice. These reports will be considered retrospective and will be reviewed separately outside of this Registry.

If a patient is exposed to multiple Registry-specified Biogen MS products within each product's eligibility window, the patient will be assigned to the product cohort according to the earliest exposure.

9.2.1.3. Registry Procedures

Reporting of pregnancy exposures to a Registry-specified Biogen MS product is voluntary. Pregnancies should be reported as early as possible, ideally before prenatal testing has been performed.

A Registry Brochure that outlines the Registry procedures and the HCP's role will be distributed to HCPs. Refer to the Registry Brochure for contact details.

Pregnancy information will be collected from the reporting Investigator or HCP by the CC to determine enrollment eligibility. The Investigator, the HCP, or the CC (where permitted by local regulations) will obtain patient consent prior to enrolling the patient into the Registry.

Patients may be included in the Registry in 1 of 3 ways, as follows:

- Spontaneous, medically-confirmed reports received by Biogen from the patient's HCP will be forwarded to the CC, *if permissible according to local regulations*; patients deemed eligible and who have given consent will be followed per the Registry Contact Schedule.
- Spontaneous reports received by Biogen from a patient will be forwarded to the CC, *if permissible according to local regulations*; patients deemed eligible and who have given consent will be followed per the Registry Contact Schedule. An HCP will be identified with whom the Registry will have contact to pursue pregnancy confirmation data.
- Any pregnancies reported in patients treated with one of the Registry-specified Biogen products in a clinical study for that product (e.g., DMF in the DMF Observational study [109MS401]) will be forwarded to the CC for inclusion in the Registry; patients deemed eligible and who have given consent will be followed per the Registry Contact Schedule. Thus, patients may be dually enrolled in the clinical study and in the Registry.

For pregnancies with outcomes that are known (i.e., pregnancy loss or live birth) at the time of the initial report (i.e., spontaneous, retrospective reports), the information will be collected and reviewed outside of this Registry by Biogen SABR according to standard postmarketing pharmacovigilance practice.

Pregnancies of partners of male-exposed patients will not be included in the Registry but will be collected according to standard postmarketing pharmacovigilance practice.

The enrollment criteria and data captured in the Registry are intended to be uniform across all countries in which the study will be conducted. Any changes to enrollment criteria or data collection imposed by a local institutional review board or ethics committee will be noted in interim and final study reports.

Oversight of the Pregnancy Exposure Registry will be the responsibility of Biogen SABR, and the Registry will be managed through the CC.

9.2.1.4. Registry Contact Schedule

After a patient provides consent, the CC Investigator will obtain demographic and contact information in addition to baseline medical history at the time of enrollment (Note: The contact information will be confidential and remain at the CC). Thereafter, the CC will contact the patient once per trimester to update contact information and ascertain the occurrence of a pregnancy outcome. The CC will contact the patient's obstetric and neurologist HCP at 6 to 7 months of gestation for the Prenatal Follow-Up and at approximately 4 weeks after the EDD for the Pregnancy Outcome Follow-Up. At approximately 4, 12, and 52 weeks after birth, the CC will contact the pediatric HCP for the Pediatric Follow-Up.

There are no mandated physician visits for this Registry.

If the patient experiences an adverse pregnancy outcome or has a therapeutic or elective pregnancy termination or an abortion of unknown cause, the HCP is encouraged, as detailed in

the Registry Brochure, to report this outcome as soon as possible rather than to wait until the scheduled follow-up contact.

See Section 9.3 and Table 5 for information collected at different periods.

9.2.2. Losses to Follow-Up

Enrolled pregnancies for which outcome information is unobtainable will be considered lost to follow-up. Before a case is considered lost to follow-up, the CC must make a minimum of 4 attempts within 3 months following the EDD to obtain pregnancy outcome information from the HCP. The CC or Biogen SABR will communicate with the HCP using the HCP's preferred contact method. If there is no response from the HCP, the CC will use other available contact methods based on past experience. Modes of communication with the HCP will include mail, fax, telephone, and e-mail. To further minimize loss to follow-up, HCPs will have the option to utilize paper or electronic case report forms (CRFs). The available modes of communication with the HCP are intended to be uniform across all countries in which the study will be conducted. Any changes to this imposed by a local institutional review board or ethics committee will be noted in interim and final study reports.

If the CC is unable to obtain the outcome of the pregnancy from the HCP, the patient or the secondary contact may be contacted for outcome information, if consistent with local regulations.

9.2.3. Registry Awareness and Outreach

9.2.3.1. Registry Awareness

Registry awareness initiatives will be implemented under Biogen SABR's guidance. The Registry will use awareness strategies that have appeared to be effective in other pregnancy exposure registry programs.

9.2.3.1.1. Outreach Efforts

Active outreach will occur to obtain reports of women exposed to a Registry-specified Biogen MS product during pregnancy.

Outreach efforts may include the following:

- discussion of the Registry with Investigators participating in Biogen MS product clinical studies, with periodic written reminders
- notification of the Registry to neurologists and other practitioners who may prescribe a Registry-specified Biogen MS product, as well as MS education and support groups, via the following:
    - the Biogen website
    - the FDA website listing pregnancy registries
    - the National Institutes of Health ClinicalTrials.gov website

- the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance website (http://www.encepp.eu/index.shtml)
- toll-free telephone number printed on a Registry-specified Biogen MS product Prescribing Information (US)
- Biogen MS Pregnancy Registry website

Apart from these potential methods of outreach, other methods will be explored as needed. All outreach methods will be approved by the appropriate review bodies as necessary.

9.2.3.2. Registry Discontinuation

9.2.3.2.1. Withdrawal of Consent

Each patient or her legally authorized representative has the right to withdraw consent from the study. A patient's participation will terminate immediately upon her request. The patient's medical data collected up until the time that consent was withdrawn will be retained and used in the Registry. If a patient is withdrawn from the Registry, Biogen SABR's routine spontaneous postmarketing surveillance follow up procedures will be followed (as required by local drug safety regulations) for any pregnancy outcomes and pregnancy-related AEs.

9.2.3.2.2. Sponsor Discontinuation of the Registry

Biogen will continue the Registry until 1 or more of the following occurs:

- Sufficient information has accumulated to meet the scientific objectives of the Registry (i.e., 300 outcomes have been observed in each product cohort). Patients with prenatal testing prior to enrollment (with the exception of a first trimester ultrasound to date the pregnancy) and their pregnancy outcomes will not be counted towards the 300 prospective pregnancy outcomes.
- The feasibility of collecting sufficient information has diminished to unacceptable levels because of low exposure rates, poor enrollment, or loss to follow-up (see Section 9.2.2 for definition of loss to follow-up).
- Other methods of gathering appropriate information (electronic medical record databases) become achievable or are deemed preferable.

Early termination of the individual cohorts or the overall study (i.e., terminated prior to observing 300 outcomes in each cohort) would occur with the agreement of the appropriate regulatory authorities.

9.3. Variables

9.3.1. Pregnancy Outcomes

9.3.1.1. Pregnancy Loss

9.3.1.1.1. Elective or Therapeutic Pregnancy Terminations

The Registry defines an elective or therapeutic pregnancy termination as any induced or voluntary fetal loss during pregnancy. If available, data from gross or pathologic examination of the abortus or fetus will be evaluated for structural or chromosomal defects.

9.3.1.1.2. Spontaneous Abortions

The Registry defines any loss of a fetus due to natural causes at <22 weeks of gestation as spontaneous abortion [EMA 2005]. If available, data from gross or pathologic examination of the abortus or fetus will be evaluated for structural or chromosomal defects. As a sensitivity analysis, spontaneous abortion will be defined as any loss of a fetus due to natural causes at <20 weeks of gestation, to be consistent with the FDA pregnancy guidance [FDA 2002].

9.3.1.1.3. Fetal Death or Stillbirth

Fetal death or stillbirth refers to the death of a fetus prior to complete expulsion or extraction from its mother at or after 22 weeks of gestation [EMA 2005]. The death is indicated by the fact that, after such separation, the fetus does not show any evidence of life (e.g., heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles). Fetal death occurring at ≥22 weeks but <28 weeks of gestation is considered an early fetal loss. Fetal death occurring at ≥28 weeks is considered a late fetal loss. As a sensitivity analysis, early fetal loss will be defined as fetal death at ≥20 weeks but <28 weeks of gestation to be consistent with the FDA pregnancy guidance [FDA 2002].

In the event of a stillbirth or maternal death, full pathology details will be requested. If available, data from gross or pathologic examination of the abortus or fetus will be evaluated for structural or chromosomal defects. The Registry will make the final classification between fetal death or stillbirth and spontaneous abortion based on gestational age. If these parameters are not available, the Registry will accept the classification indicated by the HCP.

9.3.1.2. Live Birth

A live birth refers to a complete expulsion or extraction from its mother of a surviving neonate breathing or showing any other evidence of life, such as heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles, whether the umbilical cord has been cut or the placenta is attached. Death occurring after birth will be classified as described in Sections 9.3.1.6 and 9.3.1.7.

9.3.1.2.1. Size for Gestational Age

All live births will be classified as small, appropriate, or large for gestational age using the Centers for Disease Control and Prevention definition of birth weight below the 10th percentile,

between the 10th and 90th percentile, and above the 90th percentile, respectively. An infant's birth weight percentile and categorization will be based on World Health Organization growth charts or country-specific growth charts, as appropriate.

9.3.1.3. Ectopic Pregnancies

Any reported ectopic pregnancy will be sub-classified in the respective pregnancy outcome including induced termination, maternal death, or spontaneous pregnancy loss.

9.3.1.4. Molar Pregnancies

Any reported molar pregnancy will be sub-classified in the respective pregnancy outcome including induced termination, maternal death, or spontaneous pregnancy loss.

9.3.1.5. Maternal Death

The Registry defines a maternal death as death of a pregnant woman during pregnancy, labor, or delivery. The Registry will also report maternal deaths that occur up to 12 weeks postdelivery. In the event of a maternal death, full pathology details will be requested.

9.3.1.6. Neonatal Death

The Registry defines a neonatal death as death occurring in a neonate prior to 28 days of life. In the event of a neonatal death, full pathology details will be requested. Any structural or congenital defect detected in the gross or pathologic examination of the deceased neonate will be evaluated.

9.3.1.7. Perinatal Death

The Registry defines a perinatal death as death occurring at or after 28 days of life and prior to 12 weeks of life. In the event of a perinatal death, full pathology details will be requested. Any structural or congenital defect detected in the gross or pathologic examination of the deceased neonate will be evaluated.

9.3.1.8. Infant Death

The Registry defines an infant death as death occurring between 12 and 52 weeks of life, inclusive. In the event of an infant death, full pathology details will be requested. Any structural or congenital defect detected in the gross or pathologic examination of the deceased neonate will be evaluated.

9.3.1.9. Birth Defects

All potential birth defects in the Registry from all countries will be evaluated by a qualified independent teratologist using all available medical records. The classification of all potential birth defects used in analyses will be based upon the Registry teratologist's adjudication. The exact grouping of birth defects (e.g., major versus minor defects) will vary by analysis in order to mirror the classification systems used in the selected external comparator groups.

9.3.2. Information Collected at Enrollment

Information will be collected at Enrollment, as permitted by local regulations. This information will be collected from the reporter and/or the patient and may be supplemented by information from the patient's HCP. An example of the information that will be collected is presented below:

- reporter
  - medical specialty, if HCP
- patient demographic and contact information
  - birth year and race
  - years of education
  - occupation
  - employment status
  - complete name, address, telephone number, and e-mail address*
  - name, address, telephone number, and e-mail address of a secondary contact outside of the patient's household in the case the patient cannot be contacted*

    *This information will be kept confidential and will remain at the CC (i.e., it will not be recorded on CRFs or included in the Registry database).
- maternal medical history
  - surgical and medical history
  - MS history
    - year of MS symptom onset, and year of MS diagnosis
    - current form of MS (e.g., relapsing remitting MS)
    - number of MS relapses experienced in the previous 1, 2, and 3 years
    - current use of MS therapies
    - past use of MS therapies
    - history of immunomodulatory and immunosuppressant therapies
  - family medical history
    - family history of adverse pregnancy outcomes, birth defects, congenital anomalies, and developmental delays
  - Registry-specified Biogen MS product exposure history
    - A patient's complete prior and current Registry-specified Biogen MS product exposure will be captured as a log with start and stop dates. If the exact start and stop dates are not available, the HCP or patient will provide the best approximation available (e.g., start and stop week).

*If a patient is exposed to multiple Registry-specified Biogen MS products within each product's eligibility window, the earliest product exposure will be recorded as the primary exposure and other Registry-specified products will be recorded as a concomitant medication.

- other prior (up to 6 months before conception) and current medications
- possible pregnancy outcome risk factors
  - smoking
  - caffeine
  - alcohol use
  - recreational drugs

- pregnancy history
  - previous pregnancies
    - complications
    - pregnancy outcome (e.g., live birth)
    - birth defect, congenital anomaly, or developmental delay
    - birth length and birth weight of all previous live birth infants
- current pregnancy information
  - date of LMP
  - EDD
  - method of pregnancy confirmation
  - maternal health assessments
  - prenatal testing
  - outcome (if reported retrospectively after enrollment)

9.3.3. Information Collected at Each Trimester

The CC will collect the following information from the patient or HCP at each trimester:

- changes in maternal contact information
- changes in secondary contact information
- changes in pregnancy status (if a pregnancy outcome has occurred, a pregnancy outcome assessment must be performed; Section 9.3.5)
- gestational age (in weeks)

9.3.4. Information Collected for the Prenatal Follow-Up

The CC will collect changes in the following information from the patient's HCP at approximately 6 to 7 months for the Prenatal Follow-Up*:

- maternal contact information
- secondary contact information
- pregnancy status
- gestational age (in weeks)
- prenatal testing
- maternal medical history
- current medications, including any Registry-specified Biogen MS product
- MS disease status and number of MS relapses experienced since enrollment

*If a patient is exposed to multiple Registry-specified Biogen MS products within each product's eligibility window, the earliest product exposure will be recorded as the primary exposure and other Registry-specified products will be recorded as a concomitant medication.

9.3.5. Information Collected at the Pregnancy Outcome Follow-Up

The CC will collect the following information from the patient's HCP on record, and other practitioners as needed, approximately 4 weeks after the EDD:

- pregnancy outcome (e.g., live birth, stillbirth, fetal loss, therapeutic or elective abortion)
- MS disease status and number of MS relapses experienced since the prenatal follow-up assessment until the pregnancy outcome
- infant characteristics
    - gestational age (in weeks)
    - sex
    - weight and length
    - birth order (for multiple births)
    - Apgar scores
    - any birth defect noted, including description and attribution
    - whether infant is breastfeeding

Any untoward medical occurrence related to pregnancy outcome that could constitute a serious adverse event (SAE) as defined in Section 11 will also be reported.

The CC will contact the patient's HCP earlier in the pregnancy for outcome data if the patient reports an adverse pregnancy outcome or a therapeutic abortion. Additional information and

reports will be requested and collected for adverse pregnancy outcomes in the mother and infant as necessary including autopsy and other pathology reports.

9.3.6. Information Collected at the Pediatric Follow-Up (at 4, 12, and 52 Weeks After Birth)

The following information will be collected from the infant's HCP by the CC when the infant is 4, 12, and 52 weeks of age:

- infant characteristics
    - feeding behavior
    - weight and length
    - developmental milestones
    - evidence of any abnormality not observed at 4 weeks post EDD or birth, if applicable
    - whether infant is breastfeeding

Additional information and reports will be requested and collected for adverse pregnancy outcomes in the mother (i.e., death up to 12 weeks postdelivery) and infant as necessary including autopsy and other pathology reports. Any structural defects ascertained after 12 months of age and collected in the Registry will also be reported.

9.4. Data Sources

Individual patient data will be collected as mentioned in Section 9.3. The CC will collect the Registry data from patients with MS who become pregnant while being treated with a Registry-specified Biogen MS product and from their HCPs. Reporting rates from the Registry will be compared with published reports of commercially available MS therapies from other ongoing registries and available background rates from various sources such as the EUROCAT, the ICBDSR System, and/or the March of Dimes, as appropriate (Section 9.7.3.2). Background rates generated from completed MS pregnancy registries (e.g., US Avonex Pregnancy Registry) will also be used as appropriate.

9.5. Study Size

Each Registry-specified Biogen MS product cohort will have a sufficient number of prospective, product-exposed pregnancies in patients with MS to observe 300 prospective outcome reports, where the outcome of the pregnancy is unknown at the time of the initial report. The Registry's ability to detect potential increases in risk in each cohort as compared to the expected background rates is shown in Table 3. All calculations assume that 300 pregnancy outcomes are observed and are based on a 2-sided exact test for a single proportion with $\alpha = 0.05$.

Table 3: Pregnancy Outcome Rates Used to Estimate Sample Size

Outcome	Expected Prevalence	Prevalence Rate Ratio	Power
Birth defects[1,2]	2.2%	2.9	0.80
Spontaneous abortions[3]	11%	1.52	0.81

[1] Source data: [EUROCAT 2015].
[2] The power calculation for birth defects is based on the estimated number of live births expected in the Registry, not the total number of pregnancy outcomes. The Registry assumes that 195 live births are observed out of 300 pregnancy outcomes (65% of enrolled pregnancies come to term) [Ventura 2012].
[3] Source data: [Ammon Avalos 2012].

In each cohort, it is anticipated that approximately 310 to 375 pregnant women exposed to a Registry-specified Biogen MS product will be enrolled in order to observe 300 prospective pregnancy outcomes. The planned recruitment timeline will allow for a 5% to 20% loss to follow-up and consent withdrawal.

Patients with prenatal testing prior to enrollment (with the exception of a first trimester ultrasound to date the pregnancy) and their pregnancy outcomes will not be counted towards the 300 prospective pregnancy outcomes.

9.6. Data Management

Data collection will be performed using paper or electronic CRFs. Data will be entered into a central database managed by a contract research organization (CRO).

9.7. Data Analysis

9.7.1. General Discussion of the Analysis

Analyses will be conducted separately for each cohort. Each Registry-specified Biogen MS product will have its own statistical analysis plan.

All cases will be reviewed based on earliest exposure within the associated eligibility window to a Registry-specified Biogen MS product. If a patient is exposed to multiple Registry-specified Biogen MS products within the product's eligibility window, the case will be reviewed based on the earliest exposure.

The CC and Biogen SABR will carefully review each pregnancy outcome and the calculations of risks of negative pregnancy outcomes. For this Registry, gestational weeks are calculated beginning from the first day of the LMP. If the date of LMP is not available, the EDD may be used. If the gestational week is inconsistent with the exposure dates and/or the dates of outcomes (outside 1 week for the first trimester, outside 2 weeks for the second and third trimesters) and a corrected EDD (i.e., generally by ultrasound) is available, the corrected EDD is used for gestational week calculations.

The prevalence of birth defects and spontaneous abortions and 95% confidence intervals (CIs) for the Registry population will be calculated to assess the presence or absence of any excessive

risk associated with exposure to a Registry-specified Biogen MS product. All analyses will be conducted on an overall basis, as well as stratified by earliest trimester exposure. Other negative pregnancy outcomes will be similarly examined as sample size in each cohort permits.

Any structural defects ascertained after 12 months of age and collected in the Registry will be reported but not included in the primary analysis.

In addition to the above analysis, a periodic review of the Registry will be performed by monitoring prospective and retrospective reports for each product (see Section 9.7.4).

9.7.2. Analysis Population

The primary population for analysis will be prospective reports of Registry-specified Biogen MS product-exposed pregnancies with unknown outcomes (i.e., pregnancy loss or live birth) with no informative prenatal testing at the time of the initial report. If sufficient numbers are obtained, analyses may also be conducted on subgroups of women who were exposed to multiple MS products.

Within each cohort, analyses may be conducted on subgroups to generate estimates from an analysis sample with similar characteristics to external comparator data (e.g., European Union [EU] patient subgroup analysis for comparisons with data from EUROCAT). Analyses with external comparators will not include patients with prenatal testing (other than initial screening for pregnancy confirmation).

Reports with known outcomes at the point of initial contact (i.e., retrospective reports) will be followed by Biogen SABR under standard postmarketing pharmacovigilance practice and will not be included in this Registry. Outcomes reported from patients with informative prenatal testing at the time of the initial report will be included in the Registry; these data are to be analyzed separately.

9.7.3. Methods of Analysis

Each pregnancy outcome will be classified into the categories described in Section 9.3.1.

For each interim analysis, pregnancy and infant outcomes within each cohort will be analyzed cumulatively from the beginning of the Registry.

All analyses will be conducted on an overall basis, as well as stratified by earliest trimester exposure. If sufficient numbers are obtained, analyses will also be stratified according to maternal age, gestational age at enrollment, and other important risk factors.

Demographic information, clinical characteristics, and other potential factors that may affect pregnancy outcome will be described.

The actual date of delivery (not EDD) will be used in all analyses. EDD will only be used to schedule outreach to HCPs to ascertain the outcome of an expected birth.

9.7.3.1. Pregnancy Reporting Rates

Within each cohort, the denominator for calculating reporting rates of negative pregnancy outcomes will be prospective reports, where prospective registration is defined as a report of a Registry-specified Biogen MS product-exposed pregnancy enrolled before the outcome of the

pregnancy is known (see also Section 9.9, which discusses potential biases). Retrospective reports will be tabulated separately outside of the Registry. Retrospective registration is defined as a report of a Registry-specified Biogen MS product-exposed pregnancy after the outcome of the pregnancy is known.

9.7.3.1.1. Spontaneous Abortion

Within each cohort, the prevalence of spontaneous abortions reported to the Registry will be calculated by dividing the number of fetal losses occurring at <22 weeks of gestational age by the total number of pregnancies. Sensitivity analyses will also calculate a reporting rate for fetal losses occurring <20 weeks of gestational age to conform to the FDA Pregnancy Registry guidance. The analysis of spontaneous abortions will be stratified by earliest trimester of exposure, gestational age at enrollment, maternal age, and other maternal risk factors, as appropriate.

The risk of spontaneous abortion in the Registry cohort will be examined by comparing the Registry reporting rate with a comparative general population rate observed in national or international medical or health statistics data. Age-specified rates will be examined as sample size permits.

9.7.3.1.2. Birth Defects

Within each cohort, the prevalence of birth defects reported to the Registry will be calculated using EUROCAT conventions (http://www.eurocat-network.eu/accessprevalencedata/interpretationguide/calculationofprevalencerates). The prevalence of 1 or more birth defects in addition to the prevalence of specific birth defects will be calculated as follows:

- Total Prevalence Rate = Number of Cases [Live Births + Fetal Death (>20 Weeks of Age) + Induced Abortion or Termination of Pregnancy After Prenatal Diagnosis, At Any Gestational Age] / Number of Births (Live and Still)
- Prevalence Rate at Birth = Number of Cases [Live Births + Fetal Death (>20 Weeks of Age)] / Number of Births (Live and Still)

Other formulas for prevalence rates may be used to calculate estimates used for comparisons to other background rates from other sources (e.g., March of Dimes).

Within each cohort, the analysis of birth defects outcomes will be conducted on an overall basis, as well as stratified by earliest trimester of exposure, maternal age, and other maternal risk factors, as appropriate.

Ninety-five percent CIs for birth defect rates will be calculated based on the binomial distribution.

9.7.3.2. Comparative Analyses

As appropriate and where sample size permits, birth defect reporting rates and spontaneous abortion rates from the Registry will be compared with their respective rates from published reports of commercially available MS therapies from other ongoing registries. Additional comparisons of the reporting rates from the Registry will be conducted against available

background rates from various sources such as the EUROCAT, the ICBDSR System, and/or the March of Dimes, as appropriate. Spontaneous abortion rates observed from completed MS pregnancy registries (e.g., US Avonex Pregnancy Registry, the Tysabri Pregnancy Registry) will be compared with spontaneous abortion rates in the Registry. As appropriate and where sample size permits, comparisons of the reporting rates between the products cohorts within this registry may occur. Such comparisons will include women with prenatal testing (beyond initial screening for pregnancy confirmation) as well as will be stratified by prenatal testing status. Comparison of the reporting rates between the DMF cohort and the DAC HYP cohort will occur only once the DMF cohort data have been published.

Finding an appropriate reference population for MS pregnancy outcomes is a challenge. However, using multiple external data sources, including population-based studies, national registries, and MS-specific studies, will provide high-quality information for two reasons. First, population-based studies and national registries will provide more precise background rates for rare adverse pregnancy outcomes than a concurrently enrolled active comparator group. Second, data from the US Avonex Pregnancy Registry may serve as a historical active comparator group. Prevalence rates from the US Avonex Pregnancy Registry will also be supplemented with published data from other MS pregnancy registries as they become available (e.g., the global Tysabri Pregnancy Registry and the epidemiologic study of pregnancy outcomes in unexposed Nordic patients with MS that is being developed as part of the European Interferon Beta Pregnancy Registry).

In order to minimize the differences between the comparison groups, subgroup analyses will be conducted within each cohort as appropriate on subsets of the Registry defined by factors such as age and nationality that better reflect the underlying population of the external data sources (e.g., birth defect rates in patients from the EU in comparison with data from EUROCAT). Within each cohort, comparative analyses of Registry reports will include only prospective reports (i.e., reports received before knowledge of the pregnancy outcome is known; patients who underwent informative prenatal testing are permitted to participate in the Registry). These comparisons will be based on examination of point estimates of event rates and 95% CIs. In addition to comparisons of infant outcomes (i.e., birth defects) based on events ascertained up to 52 weeks post-birth, comparisons will also be based on infant outcomes ascertained up to 12 weeks postbirth in order to mirror the ascertainment period used in previous Biogen pregnancy registries.

9.7.4. Interim Analyses

Within each cohort, data from the Registry will be assessed at least annually in descriptive summary reports and in routine safety aggregate reports (e.g., Periodic Safety Update Reports). For each interim analysis, pregnancy and infant outcomes will be analyzed cumulatively from the beginning of the Registry.

In addition to the above analysis, a periodic review of each cohort within the Registry will be performed by monitoring prospective and retrospective reports. The Registry will adopt the "Rule-of-Three" convention defined as when 3 or more individual birth defects, which appear to be the same both structurally and physically, and which have the same exposure, are detected in a single cohort [Covington 2004]. These cases will be flagged for immediate review by Biogen SABR personnel. The rationale for choosing a threshold of 3 events is because the likelihood

(using exact probability statistics) of finding at least 3 of any specific defect in a single cohort of 300 or fewer by chance alone is <5% for all but the most common defect classes (i.e., those occurring with a rate <1/700). For example, in 300 women exposed to a regimen it would not be at all unusual to find at least 3 defects classified as "heart and circulation," or "nervous system and eye," but it would be unusual to find 3 classified as club foot or as cleft lip.

9.7.5. Independent Advisors

A qualified independent teratologist or other appropriate birth defect evaluator, for evaluation of birth defects and other significant findings, will be used throughout the Registry. An independent Advisory Board will review pregnancy outcome data on an annual basis. A separate meeting will be convened for each cohort. Biogen will also consult other experts in relevant specialties, if deemed necessary by the external advisors. The Advisory Board will review all analyses prior to submission of interim reports for each cohort.

9.7.6. Postmarketing Cases

Biogen will also present a summary of all postmarketing cases identified in routine product periodic safety update reports.

9.8. Quality Control

9.8.1. Quality Assurance

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform on-site audits. The physician will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

9.8.2. Monitoring of the Study

Biogen or designee representatives may conduct onsite visits at the study facilities for the purpose of monitoring various aspects of the study. The physician must agree to Sponsor-authorized personnel having direct access to the patient (or associated) files for the purpose of verifying entries made in the CRF, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the HCP or study staff. The site must complete the CRFs in a timely manner and on an ongoing basis to allow regular review by the study team.

9.9. Limitations of the Research Methods

Although measures will be taken to ensure the Registry has robust data collection, certain limitations should be acknowledged.

Estimating an accurate rate of early spontaneous pregnancy losses is difficult in voluntary pregnancy registries. Spontaneous losses are likely to occur before the pregnancy is recognized. Even if the pregnancy is recognized, it may not be reported to the Registry if the spontaneous loss occurred prior to Registry enrollment. As such, there will likely be a reporting bias leading to an underestimation of the true early pregnancy loss rate. Excluding pregnancies whose

outcome is known prior to registration may introduce a selection bias that also underestimates the true rate of early pregnancy losses. To address these biases, the Registry will evaluate pregnancy losses within each cohort as a function of gestational age at enrollment into the Registry. In addition, the rates of spontaneous pregnancy loss within each cohort will be compared to other pregnancy registries in MS patients with similar reporting rules. The study design of the Biogen MS Pregnancy Registry is similar to other pregnancy studies in MS (e.g., Avonex and Tysabri pregnancy registries). There is no reason to believe these studies will be differentially impacted by the aforementioned biases. As such, even though the absolute rate of spontaneous losses and early adverse pregnancy outcomes within each cohort may be underestimated, the relative rate compared to other voluntary registries should remain valid. Finally, pregnancy outcomes that occur outside the Registry will be collected as part of routine pharmacovigilance practice. These spontaneous reports will be analyzed for each Registry-specified Biogen MS product to determine if there is a signal for an increased risk of adverse early pregnancy outcomes including spontaneous pregnancy losses.

Reporting pregnancy outcomes is voluntary and it is possible that not all participants will complete all follow-up assessments. Enrolled pregnancies for which outcome information is unobtainable will be considered lost to follow-up. It is possible that outcomes from pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in follow-up and reporting patterns, it is currently not possible to assess with any certainty what effect the potential biases of the loss to follow-up may have on the analysis. However, comparisons of the characteristics of each group will be conducted in an attempt to address this potential source of bias.

Background rates will be obtained from previously completed MS pregnancy registries and other pregnancy outcome surveillance projects (e.g., the EUROCAT), but biases introduced by design differences across studies must be acknowledged. The proposed design for the Biogen MS Pregnancy Registry is very similar to the Avonex and Tysabri pregnancy registries conducted in MS. Large differences in the distribution of important risk factors such as maternal age between the Biogen MS Pregnancy Registry and other data sources would need to be considered when making comparisons. Given the limitations in available pregnancy outcome data sources, the Sponsor and the independent advisory board will interpret the results of each cohort with the Biogen MS Pregnancy Registry using multiple external data sources, noting the strengths and limitations of each comparison. Inclusion of patients with prenatal testing may introduce bias into the study. Therefore, some analyses may be stratified by prenatal testing status at enrollment.

9.10. Other Aspects

9.10.1. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, physician, and Biogen.

9.10.2. Publications

Details are included in the clinical study agreement for this study.

10. PROTECTION OF HUMAN SUBJECTS

Biogen and participating HCPs must comply with this protocol and applicable International Council for Harmonisation and Good Pharmacovigilance Practices guidelines, and conduct the study according to local regulations. The patient's privacy; physical, mental, and social integrity; and the confidentiality of his or her personal information will be strictly respected in accordance with the World Medical Association Declaration of Helsinki.

10.1. Ethics Committee

Participating physicians must obtain centralized and/or local ethics committee approval of the protocol, informed consent form (ICF), and other required study documents prior to starting the study. The CRO (Section 3) will submit documents on behalf of the study sites in countries as agreed to with the Sponsor.

If the physician makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

It is the responsibility of the physicians to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

Biogen must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol. Where necessary, the national regulatory authority will be notified about the Registry.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, the study site must submit a close-out letter to the ethics committee and Biogen.

10.2. Subject Information and Consent

Patient consent (written or verbal per local regulations) must be obtained by the reporting HCP, Investigator, or CC (if permitted by local regulations) prior to the patient's enrollment in the Registry. If the patient is a minor, written consent must be obtained from the parent or legal guardian. A Release of Medical Information will be obtained from the patient to permit the CC to contact HCPs related to the pregnancy (e.g., the patient's obstetric HCP) to follow up on the patient according to the schedule as defined in Section 9.3.2, Section 9.3.3, Section 9.3.4, and Section 9.3.5. In addition, a Release of Medical Information will also be obtained by the enrolling HCP from the parent or the infant's Personal Representative so that the CC can contact the pediatric HCP to follow up on the infant according to the schedule (defined in Section 9.3.6).

10.3. Changes to Final Registry Protocol

The ethics committee and appropriate regulatory authorities will be contacted, as applicable, about changes to the protocol.

10.4. Subject Data Protection

Prior to any data collection under this protocol, patients must also provide all authorizations required by local law (e.g., protected health information authorization in North America).

The patient will not be identified by name in the CRF or in any study reports, and these reports will be used for research purposes only. Biogen and designee(s), ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the patient's personal medical data confidential.

10.5. Internal Safety Review

SABR and other applicable personnel at Biogen will review all SAEs related to pregnancy or pregnancy outcomes on a regular basis.

11. SAFETY DEFINITIONS AND REPORTING

Only SAEs related to pregnancy and/or pregnancy outcomes are required to be recorded under this protocol using the appropriate SAE Report Form.

An SAE **in this study** is any untoward medical occurrence related to pregnancy and/or pregnancy outcome that at any dose:

- results in death
- in the view of the reporting HCP, places the patient or infant at immediate risk of death (a life-threatening event; however, this does not include an event that, had it occurred in a more severe form, might have caused death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is an important and significant medical event that, in the opinion of the reporting HCP, may jeopardize the patient or infant, or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home, which do not require an inpatient hospitalization
- is a pregnancy outcome of spontaneous abortion, fetal loss including stillbirth, ectopic pregnancy, molar pregnancy, elective or therapeutic pregnancy terminations, birth defects/congenital anomaly, or premature births

Obstetric complications that fall into these categories are defined as serious and should be reported to this Registry.

If the pregnant patient reports any non-pregnancy-related SAEs, these SAEs must be forwarded to Biogen SABR or its designee to process as a spontaneous report; if the patient is enrolled in another Biogen study, these SAEs should be handled under the relevant protocol. The CC will consult with Biogen SABR for any questions regarding whether an SAE is pregnancy related.

Nonserious AEs, pregnancies, and other safety information not falling under this protocol should be reported outside this Registry following standard pharmacovigilance practices.

In addition, normal delivery and elective C-sections performed for non-medical reasons (i.e., scheduling, personal preference) and their related hospitalizations will not be considered SAEs, unless, in the view of the reporting HCP, the hospitalization was prolonged due to a complication.

The reporting HCP must assess the relationship of the pregnancy-related SAE to a Registry-specified Biogen MS product on an SAE Report Form. The definitions for relationships can be found in the following table.

Relationship of Event to a Registry-Specified Biogen MS Product	
Not related	An adverse event will be considered "not related" to the use of a Registry-specified Biogen MS product if there is not a possibility that the event has been caused by a Registry-specified Biogen MS product. Factors pointing toward this assessment include, but are not limited to, the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the adverse event (e.g., the event occurred before administration of drug), or the presence of a more likely alternative explanation for the adverse event.
Related	An adverse event will be considered "related" to the use of a Registry-specified Biogen MS product if there is a possibility that the event may have been caused by a Registry-specified Biogen MS product. Factors that point toward this assessment include, but are not limited to, a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the adverse event, or a lack of an alternative explanation for the adverse event.

Pregnancy-related SAEs will be reported to the CC, and follow-up will be obtained as needed by the CC.

To report initial or follow-up information on a Serious Pregnancy-Related Event, fax a completed SAE Report Form to the following:
Refer to the Investigator Site File for country-specific fax numbers and email information.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Reporting of Pregnancy Data to Health Authorities

Data from the Registry will be assessed annually in descriptive summary reports and in routine safety aggregate reports (e.g., Periodic Safety Update Reports).

12.2. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

12.3. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

13. REFERENCES

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14. ANNEX 1: LIST OF STAND ALONE DOCUMENTS

Table 4: List of Stand-Alone Documents for Protocol 109MS402

Number	Document Reference Number	Date	Title
None			

15. ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 2)

Adopted by the ENCePP Steering Group on 14th January 2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☒	☐	
1.1.2 End of data collection[2]	☐	☒	☐	
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☐	☒	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	1,11,21
2.1.2 The objective(s) of the study?	☒	☐	☐	1,11,21
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	10,12,19-20,21,22
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

The Pregnancy Exposure Registry is being conducted as part of routine pharmacovigilance. No a priori hypothesis is being tested.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	12,22,23
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	11,22,23
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	14,34-35

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	12,23-25
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☐	☒	☐	
4.2.2 Age and sex?	☒	☐	☐	11,12,23,24
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	1,10,19-20, 21,22,23
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	12,23-25

Comments:

The Pregnancy Exposure Registry will evaluate women of child-bearing potential with MS. Otherwise there will be no restrictions on enrollment in terms of age, county of origin, study time period, or co-morbidity. The goal of this study is to recruit a sample reflective of MS patients prescribed DMF as part of routine clinical care. Recruitment will span multiple years, thus we do not anticipate seasonality effects due to date of enrollment.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	11,22,28-29
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	34,35
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Pregnant women with MS will be eligible to enroll in this study if they have been exposed to DMF since the first day of their last menstrual period and if other eligibility criteria are met. This time frame was based on the pharmacokinetic profile of DMF (The half-life of DMF is 12 minutes and that of its active metabolite MMF is 36 hours). By definition all patients will have at least one dose of DMF. Some analyses will be stratified by trimester of exposure. Analyses will be further stratified by other exposure metrics (e.g. duration of exposure) as data permits. Details on the collection of DMF prescription and dosing information and the analysis of outcomes with respect to DMF exposure will be described in the statistical analysis plan and the clinical study report.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	28-29
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	34-37

Comments:

In this study, endpoints are defined according to US and EU regulatory guidance documents. A teratologist will evaluate and classify all potential birth defects and an independent advisory board will review all negative birth outcomes.

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	34,35,36-38
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments:

There are no known effect modifiers with respect to pregnancy outcomes and DMF exposure. As data permits, collected confounders will be explored as potential effect modifiers if descriptive analyses suggest a potential relationship.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	23-24,25-26,30-33
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	23-24,25-26,30-33
8.1.3 Covariates?	☒	☐	☐	23-24,25-26,30-33
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	30-33
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	30-33
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	30-33
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Pregnancy outcomes will be defined per protocol. MedDRA will be used to classify other medical events. Drug exposure will be described using Biogen standards (e.g. WHO Drug Dictionary). A detailed description of the information collected in this study (e.g., exposure, covariates) as well as coding systems will be provided in the clinical study report.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	13,33,34

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	14,34,35-36
10.4 Are stratified analyses included?	☒	☐	☐	34,35-36
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	35-37
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

As data permit, stratified analyses will be the main method for adjusting for confounding. A detailed description of the statistical analyses used to analyze study data will be provided in the statistical analysis plan which will be included in the clinical study report.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☒	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	38
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	38,39
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	38

Comments:

Data management for this study will be performed by a vendor selected by Biogen, and in a manner consistent with internal Biogen quality standards. Details will be provided in the final clinical study report.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	38,39
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	38,39
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	38,39

Comments:

Biogen has successfully completed two previous pregnancy registries of similar size and scope in MS patients.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	40
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	41

Comments:

This study has been approved by an Investigational Review Board in the United States but has yet to be submitted for ethical review in other countries.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	15

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	42
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	39,42

Name of the main author of the protocol: [redacted], PhD

Date: / /

Signature: _____

16. ANNEX 3: ADDITIONAL INFORMATION

Table 5: Registry Contact Schedule

Data Collection	Enrollment	Prenatal Follow-Up		Pregnancy Outcome Follow-Up	Pediatric Follow-Up
	Initial Report/Registration by Patient With CC [1]	CC Contact With the Patient at Each Trimester	CC Contacts HCP at 6 to 7 Months of Gestation	CC Contacts HCP(s) at Approximately 4 Weeks After EDD [2]	CC Contacts Infant's HCP at Approximately 4, 12, and 52 Weeks of Age [3]
Patient Consent [4]	X				
Patient Demographics	X				
Patient Contact Information	X	X			
Medical History	X		X		
Pregnancy History, Current Pregnancy Information, Possible Risk Factors [5]	X		X		
Current Pregnancy Status		X	X		
Gestation Age (in Weeks)		X	X	X	
Registry-Specified Biogen MS Product Use [6]	X		X		
Prior and Current Medications Other Than a Registry-specified Biogen MS Product [6] (Throughout Pregnancy)	X [7,8]		X [8]		
MS Disease Status and Number of MS Relapses Experienced			X [9]	X [10]	

Data Collection	Enrollment	Prenatal Follow-Up		Pregnancy Outcome Follow-Up	Pediatric Follow-Up
	Initial Report/Registration by Patient With CC [1]	CC Contact With the Patient at Each Trimester	CC Contacts HCP at 6 to 7 Months of Gestation	CC Contacts HCP(s) at Approximately 4 Weeks After EDD[2]	CC Contacts Infant's HCP at Approximately 4, 12, and 52 Weeks of Age[3]
Pregnancy Outcome				X	
Infant Characteristics				X[11]	X[12]
Evidence of Any Abnormality Not Identified at Birth (if Applicable)					X
Serious Adverse Events (Pregnancy-Related)	Record throughout the final patient and infant contact.				

CC = coordinating center; DAC HYP = daclizumab high yield process; DMF = dimethyl fumarate; EDD = estimated date of delivery; HCP = health care provider; MS = multiple sclerosis

'If a patient is exposed to multiple Registry-specified Biogen MS products within each product's eligibility window, the earliest product exposure will be recorded as the primary exposure and other Registry-specified products will be recorded as a concomitant medication.

Error! Reference source not found. A Registry-specified Biogen MS Product is a marketed Biogen MS product specified in this Pregnancy Registry (DMF or DAC HYP).

[1] Additional contact will be made with the patient's HCP to obtain medical information.

[2] If a patient experiences an adverse pregnancy outcome or has a therapeutic or elective pregnancy termination or an abortion of unknown cause, the HCP is encouraged to report this outcome as soon as possible.

[3] The CC will contact the infant's HCP, designated either at enrollment or during one of the previous collection periods.

[4] Patient consent (written or verbal per local regulations or ethics committee requirements) must be obtained prior to the patient's enrollment. If the patient is a minor, written consent must be obtained from the parent or legal guardian. A Release of Medical Information will also be obtained by the enrolling HCP from the parent or the infant's Personal Representative so that the CC can contact the pediatric HCP for the 4-, 12-, and 52-week follow-up.

[5] To include a detailed family history, including adverse pregnancy outcomes and developmental abnormalities, and information about baseline risks. Risk factors include smoking, use of caffeine, use of alcohol, and use of recreational drugs.

[6] A Registry-specified Biogen MS Product is a marketed Biogen MS product specified in this Pregnancy Registry (DMF or DAC HYP).

[7] Current medications and past medications up to 6 months prior to conception.

[8] If a patient is exposed to multiple Registry-specified Biogen MS products within each product's eligibility window, the earliest product exposure will be recorded as the primary exposure and other Registry-specified products will be recorded as a concomitant medication.

[9] MS disease status and number of MS relapses experienced since enrollment.
[10] MS disease status and number of MS relapses experienced since the prenatal follow-up assessment until the pregnancy outcome.
[11] Gestational age, sex, weight, length, birth order (for multiple births), Apgar scores, breastfeeding status, and any birth defect noted, including description and attribution.
[12] Feeding behavior, weight, length, developmental milestones, breastfeeding status, and evidence of any abnormality, if applicable.