TITLE:	**OCRELIZUMAB PREGNANCY REGISTRY**
PROTOCOL NUMBER:	WA40063
VERSION NUMBER:	1.0
AUTHOR:	[redacted] F. Hoffman-La Roche Ltd 4070 Basel Switzerland
DATE FINAL:	See electronic date stamp below
EU PAS REGISTER NUMBER:	Study not registered
ACTIVE SUBSTANCE:	[redacted] (ocrelizumab)
STUDIED MEDICINAL PRODUCTS:	OCREVUS® glatiramer acetate
PRODUCT REFERENCE NUMBER:	RO4964913
PROCEDURE NUMBER:	IND 100,593; BLA 761053
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	To assess and characterize frequency of maternal, fetal, and infant outcomes among women with multiple sclerosis (MS) exposed to ocrelizumab during the 6 months before the estimated date of conception or at any time during pregnancy.

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	15-Apr-2019 10:06:15
	Deputy EU QPPV	12-Apr-2019 13:17:27

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	The objectives for this registry are as follows: • To estimate the frequency of selected adverse pregnancy outcomes (i.e., spontaneous abortions, stillbirths, elective terminations, and preterm births) in women with MS exposed to ocrelizumab during the defined exposure window • To estimate the frequency of selected adverse fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, small for gestational age, postnatal growth and development, and outcomes related to immune suppression) at birth and through at least the first year of life of infants from pregnancies in women with MS exposed to ocrelizumab during the defined exposure window • To compare the maternal, fetal, and infant outcomes of women with MS exposed to ocrelizumab with two unexposed control populations: one consisting of women with MS who have not been exposed to ocrelizumab before or during pregnancy and the other consisting of women without MS
COUNTRIES OF STUDY POPULATION:	United States, Germany, and other potential countries
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH (RRG) Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
MAH CONTACT PERSON:	[redacted] Roche Products Ltd 6 Falcon Way Welwyn Garden City AL7 1TW United Kingdom

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PROTOCOL ACCEPTANCE FORM

TITLE:	**OCRELIZUMAB PREGNANCY REGISTRY**
PROTOCOL NUMBER:	WA40063
VERSION NUMBER:	1.0
EU PAS REGISTER NUMBER:	Study not registered
STUDIED MEDICINAL PRODUCTS:	ocrelizumab (RO4964913; OCREVUS®) glatiramer acetate
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH (RRG) Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany

I agree to conduct the study in accordance with the current protocol.

_____
Coordinating Center Investigator Name (print)

_____ _____
Coordinating Center Investigator Signature Date

Please return a copy of this form to [redacted]. Please retain the signed original for your study files.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BMI	body mass index
CC	coordinating center
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CNS	central nervous system
CRO	contract research organization
DMT	disease-modifying therapy
eCRF	electronic Case Report Form
EDC	electronic data capture
EDD	expected date of delivery
EDSS	Expanded Disability Status Scale
E.U.	European Union
EUROCAT	European Surveillance of Congenital Anomalies
FDA	(U.S.) Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
IEC	independent Ethics Committee
IgG1	immunoglobulin G1
IRB	Institutional Review Board
LMP	last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	marketing authorization holder
MS	multiple sclerosis
MSIF	Multiple Sclerosis International Federation
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	odds ratio
PAS	post-authorization study
PBRER	periodic benefit-risk evaluation report
PMR	postmarketing requirements
PPMS	primary progressive multiple sclerosis
RMS	relapsing forms of multiple sclerosis

Abbreviation	Definition
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDV	source data verification
SPMS	secondary progressive multiple sclerosis
U.S.	United States

3. RESPONSIBLE PARTIES

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4. SYNOPSIS

TITLE:	**OCRELIZUMAB PREGNANCY REGISTRY**
PROTOCOL NUMBER:	WA40063
VERSION NUMBER:	1.0
DATE OF SYNOPSIS:	See electronic date stamp on the cover page

Rationale and Background

Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system (CNS) that affects approximately 2.3 million people worldwide (MSIF 2013). While MS is a global disease, the prevalence of MS is highest in North America and Europe (140 and 108 per 100,000, respectively) (MSIF 2013). MS is commonly diagnosed during reproductive age, between 20–40 years (Tullman 2013). Overall, women are affected approximately twice as often as men, except in individuals with the primary progressive multiple sclerosis (PPMS), where there is no gender prevalence difference (Tullman 2013; MSIF 2013). Reasons for these observed differences are unclear.

In approximately 85% of patients, MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery (relapsing remitting MS [RRMS]). If left untreated, the majority of these patients will transition to a progressive form characterized by worsening neurologic disability either with or without occasional superimposed relapses (relapsing or non-relapsing secondary progressive MS [SPMS]). Patients accumulate disability as a result of incomplete recovery from acute relapses and/or gradual disease progression (Tullman 2013). PPMS is a less common form of MS, accounting for approximately 10% of all cases (approximately 40,000 individuals in the United States). It is characterized by a progressive course from disease onset, with infrequent superimposed discrete clinical attacks or relapses (Lublin 2014).

Evidence suggests that inflammation is present in the CNS throughout all MS clinical courses, from RRMS to SPMS and in PPMS (Frischer et al. 2009). Differences between disease phenotypes are due to the differential contribution of each of the inflammatory and neurodegenerative processes to the pathophysiology of CNS damage over time (Frischer et al. 2009; Frischer et al. 2015).

OCREVUS® (ocrelizumab) was approved by the U.S. Food and Drug Administration (FDA) on March 28, 2017, for the treatment of adult patients with relapsing forms of MS (RMS) and PPMS (Genentech Inc. 2017). Subsequently, OCREVUS was approved in the European Union (E.U.) (including Germany), Switzerland, Australia, Canada, and several other countries.

Ocrelizumab is a recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody that selectively targets CD20-expressing B cells. Two identical, randomized, active-controlled studies (OPERA I [Study WA21092] and OPERA II [Study WA21093]) have demonstrated superior efficacy outcomes versus interferon β-1a in RMS (Hauser et al. 2017); one randomized placebo-controlled study (ORATORIO [Study WA25046]) has demonstrated superior efficacy in PPMS versus placebo (Montalban et al. 2017).

Immunoglobulins, such as ocrelizumab, are known to cross the placental barrier. B-cell levels in human neonates following maternal exposure to ocrelizumab have not been studied in clinical studies. There are no adequate and well-controlled data from studies in pregnant women; however transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy (Chakravarty et al. 2011; Klink et al. 2008).

It is not known whether ocrelizumab can affect pregnancy outcomes or infant outcomes in humans. However, based on pathophysiological considerations, ocrelizumab might theoretically affect pregnancy outcomes and infant outcomes in the following ways:

- By direct exposure of the fetus to ocrelizumab, which is assumed to occur after the 16th week of gestation as receptor-mediated transplacental transfer of IgG1; this is minimal during the first trimester of pregnancy (Palmeira et al. 2012; Simister 2003)
- Indirectly due to known or unknown infections or infectious complications in the mother exposed to ocrelizumab during pregnancy, which may affect the offspring, where the infection may be associated with ocrelizumab exposure
- Indirectly due to effects of ocrelizumab on the placenta

The Ocrelizumab Pregnancy Registry will be conducted to fulfill part of the FDA postmarketing requirements (PMR) (3194-3) for approval of ocrelizumab in the United States.

Research Question and Objectives

To assess and characterize frequency of maternal, fetal, and infant outcomes among women with MS exposed to ocrelizumab during the 6 months before the estimated date of conception or at any time during pregnancy.

Objectives

The Ocrelizumab Pregnancy Registry is designed to address the FDA PMR with the following objectives:

- To estimate the frequency of selected adverse pregnancy outcomes (i.e., spontaneous abortions, stillbirths, elective terminations, and preterm births) in women with MS exposed to ocrelizumab during the defined exposure window
- To estimate the frequency of selected adverse fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, small for gestational age, postnatal growth and development, and outcomes related to immune suppression) at birth and through at least the first year of life of infants from pregnancies in women with MS exposed to ocrelizumab during the defined exposure window
- To compare the maternal, fetal, and infant outcomes of women with MS exposed to ocrelizumab with two unexposed control populations: one consisting of women with MS who have not been exposed to ocrelizumab before or during pregnancy and the other consisting of women without MS

Study Design

This is a prospective observational registry that will collect primary data from 290 pregnant women (153 pregnancy outcomes) with MS from the United States, Germany, and other potential countries, who have been exposed to ocrelizumab during the 6 months prior to their last menstrual period (LMP) or at any time during pregnancy.

The frequencies of outcomes will be presented in comparison to both existing databases and an internal comparator group.

Description of Study

Data will be collected from patients and their healthcare providers (HCPs) (e.g., neurologist, obstetrician) during pregnancy and through at least 1 year after birth (infant's HCP and/or the patient). The registry is voluntary and any currently pregnant woman with MS exposed to ocrelizumab, as defined above, will be eligible. The internal comparator group will consist of currently pregnant women with MS who were not exposed to any MS disease-modifying therapies (DMTs) during the 6 months prior to their LMP or at any time during pregnancy (apart from glatiramer acetate [e.g., Copaxone] exposure through the first trimester). Internal comparator patients will be enrolled from the same sites as the ocrelizumab-exposed women and follow the same study procedures for follow-up and data collection. The total duration of participation is up to 21 months, and the total duration of the study is approximately 10 years.

Population

Patients must meet the following criteria for study entry:

- Patient consent (written or verbal per local regulations or Ethics Committee requirements) obtained prior to enrollment. If the patient is a minor, written consent must be obtained from their parent or legal guardian. Consent will be obtained in compliance with any country-specific regulations or requirements.
- Currently pregnant
- Diagnosed with MS
- Ocrelizumab-exposed group: Pregnant women with MS with documentation that the patient was exposed to ocrelizumab at any point starting from 6 months prior to LMP
- Internal comparator group, which includes:
  - Pregnant women with MS with documentation that the patient was not exposed to any MS DMTs during the 6 months prior to their LMP or at any time during their pregnancy

    OR
  - Pregnant women with MS with documentation that the patient was exposed to glatiramer acetate during the 6 months prior to their LMP through the first trimester
- Agrees to sign the Release of Medical Information Form permitting the study to contact her HCP(s) and the pediatric HCP for medical information
- The outcome of the pregnancy (i.e., pregnancy loss or live birth) must not be known.

Women who have had prenatal testing prior to enrollment that could determine the status of the fetus (e.g., amniocentesis, genetic testing, nuchal translucency screen, chorionic villus sampling, and late term ultrasound) will be considered prospective cases. However, the primary data analysis will exclude women who have received first trimester prenatal screening in which either aneuploid disorders or genetic disorders that cause major congenital malformations have been detected. Retrospective cases include women where the pregnancy outcome is known, prior to enrollment in the registry, either positive or negative, for major congenital malformations that are unrelated to genetic or aneuploid disorders. Retrospective cases will be analyzed separately for both primary and secondary analysis.

No exclusion criteria will apply for this study.

Variables

The following variables will be collected during the study, as part of the local routine clinical practice, as available:

Baseline:

- Documentation of informed consent
- Reporter of information (patient, obstetrician, neurologist)
- Patient demographics and characteristics (e.g., age of mother and father, education level, race/ethnicity, height, weight, body mass index)
- Patient, secondary contact, and HCP contact information (obstetrician, neurologist, infant HCP, if possible)
- Lifestyle risk factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)
- Current pregnancy information (e.g., LMP, gestational age, expected date of delivery [EDD], date and results of any prenatal tests)

- Maternal medical history:
  - Pregnancy history (e.g., parity, gravidity, previous preterm births, previous spontaneous abortions or elective or therapeutic terminations, reason for any elective or therapeutic termination, history of congenital malformations)
  - Surgical and medical history/significant maternal medical conditions other than MS (e.g., diabetes, high blood pressure)
  - MS disease history (including MS subtype and treatment history such as glatiramer acetate, disease duration, most recent Expanded Disability Status Scale [EDSS] score, if available)
  - Comorbid conditions
  - Family reproductive history (e.g., multiple births, congenital malformations, spontaneous abortions, premature births, chromosomal anomalies, developmental delays)
  - Family MS history
  - Ocrelizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable])
  - Current and prior medication use from 6 months prior to conception (including other MS treatments such as glatiramer acetate, teratogenic medications, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic disease)

Follow-up during pregnancy (during each trimester, approximately at 14, 21, and 34 weeks gestation):

- Date of contact
- Reporter of information (patient, obstetrician, neurologist)
- Changes in contact information (maternal, secondary contact, and HCP)
- Changes in pregnancy status:
  - Gestational age
  - Any prenatal testing performed and results (e.g., rubella titer, toxoplasmosis, venereal disease research laboratory test, hepatitis screen, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein screen, glucose screen)
  - Pregnancy outcome, if applicable (e.g., elective or therapeutic termination, spontaneous abortion, ectopic pregnancy, molar pregnancy)
    - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
    - Autopsy results and pathology reports, if available
- Changes in MS disease status (including treatment changes, relapses, EDSS score)
- Ocrelizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable])
- Changes in comorbid conditions
- Current lifestyle risk factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)
- Current medications (including other MS treatments such as glatiramer acetate, teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)
- Serious adverse events (SAEs) related to pregnancy (see protocol definition)

Birth outcome follow-up (approximately 4 weeks after EDD):

- Date of contact and date of pregnancy outcome or gestational age (in weeks)
- Changes in contact information; contact information for infant's HCP
- Reporter of information (patient, obstetrician, infant HCP)
- Pregnancy outcome (e.g., live birth, stillbirth, spontaneous abortion, elective or therapeutic termination)
  - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
  - Autopsy results and pathology reports, if available
- Mode of birth (vaginal delivery, assisted delivery/cesarean section, type of anesthesia)
- MS disease and treatment status since last follow-up
- Ocrelizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable])
- Changes in comorbid conditions
- Current lifestyle factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)
- Current medications (including other MS treatments such as glatiramer acetate, teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)
- Infant characteristics:
  - Gestational age at birth
  - Sex
  - Weight
  - Length
  - Head circumference
  - Birth order (for multiple births), and number of fetuses
  - Laboratory values, if available (e.g., CD19, neutrophil, lymphocyte, white blood cell, immunoglobulin, and platelet counts)
  - Apgar scores (1, 5, and 10 minutes)
  - Congenital malformations noted (including description and attribution)
  - Vaccination information
  - Whether infant is breastfed
- SAEs related to pregnancy (see protocol definition)
- All infant SAEs (including serious and severe infections of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) severity Grade 3, 4 or 5 and hospitalizations other than for standard post-birth hospital stay)

Pediatric follow-up (approximately at infant age 12, 26, and 52 weeks after birth):

- Reporter of information (patient, obstetrician, infant HCP)
- Infant characteristics:
  - Feeding behavior (including breastfeeding)
  - Weight
  - Length
  - Head circumference

    - Developmental milestones (e.g., social/emotional, language/communication, cognitive, movement/physical development milestones, as defined by the Centers for Disease Control and Prevention [CDC 2016])
    - Laboratory values, if available (e.g., CD19, neutrophil, lymphocyte, white blood cell, immunoglobulin, and platelet counts)
    - Evidence of any new congenital malformations and growth alterations since last follow-up
    - Vaccination information
- All infant SAEs (including serious and severe infections of NCI CTCAE severity Grade 3, 4 or 5 and hospitalizations other than for standard post-birth hospital stay)

Early termination of study participation contact, if applicable:

- Reporter of information (patient, obstetrician, infant HCP)
- Assessments appropriate for the time of withdrawal
- Reason for study withdrawal
- Ocrelizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable])
- Other medications (including other MS treatments such as glatiramer acetate, teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)
- Pregnancy status:
    - Gestational age
    - Any prenatal testing performed and results (e.g., rubella titer, toxoplasmosis, venereal disease research laboratory test, hepatitis screen, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein screen, glucose screen)
    - Pregnancy outcome, if applicable (e.g., elective or therapeutic termination, spontaneous abortion, ectopic pregnancy, molar pregnancy) as per Section 9.3.2
    - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
    - Autopsy results and pathology reports, if available
- Infant characteristics (for live births):
    - Gestational age at birth
    - Sex
    - Weight
    - Length
    - Head circumference
    - Birth order (for multiple births), and number of fetuses
    - Laboratory values, if available (e.g., CD19, neutrophil, lymphocyte, white blood cell, immunoglobulin, and platelet counts)
    - Apgar scores (1, 5, and 10 minutes)
    - Congenital malformations noted (including description and attribution)
    - Whether infant is breastfed, if applicable
- SAEs related to pregnancy, pregnancy outcomes, and/or infant SAEs (including serious and severe infections of NCI CTCAE severity Grade 3, 4, and 5 and hospitalizations other than for standard post-birth hospital stay)

Data Sources

Data will be obtained through questionnaires administered to patients and their HCPs (neurologist, obstetrician, and infant HCP).

Study Size

Assuming a 15% drop-out rate and a live birth rate of 62% (FDA 2002; Ventura et al. 2000), 290 ocrelizumab-exposed pregnant women with MS will need to be enrolled to observe 153 pregnancy outcomes. This sample size provides 80% power to detect a relative risk of 2.5 or greater in major congenital malformations relative to the baseline prevalence of 3% in the external comparator (CDC 2008) at a significance level of α=0.05.

In addition to the external comparator, the internal comparator group will enroll approximately 290 pregnant women to support the study objective to compare the maternal, fetal, and infant outcomes of women with MS who have not been exposed to ocrelizumab before or during pregnancy.

Data Analysis

The primary outcome of interest for this study are major congenital malformations, and other outcomes are classified as secondary. The overall frequency (proportion, 95% CI) of selected adverse pregnancy outcomes will be calculated, as well as frequencies of specific outcomes, e.g., spontaneous abortions, stillbirths, elective or therapeutic terminations, and preterm births. The same will be calculated for selected adverse fetal, neonatal, and infant outcomes at birth and through at least the first year of life of infants (i.e., major and minor congenital malformations, small for gestational age, postnatal growth and development, and outcomes related to immune suppression). The European Surveillance of Congenital Anomalies (EUROCAT) birth defects classification system will be used to characterize adverse pregnancy outcomes for this study.

All analyses will be conducted on an overall basis, as well as presented by enrollment type (i.e., prospective versus retrospective cases; see Section 9.2.2) and by earliest trimester of ocrelizumab exposure. If sufficient numbers are obtained, analyses will also be presented by maternal age, race/ethnicity, gestational age at enrollment, elective or therapeutic pregnancy termination status, prenatal screening result (positive versus negative), glatiramer acetate exposure (internal comparator group), and other important risk factors. Prevalence and associated 95% CIs will be calculated.

Similar descriptive analyses summarized above will be performed on the internal comparator group consisting of pregnant women with MS who were not exposed to any MS DMTs (apart from glatiramer acetate). The internal comparator group will be analyzed overall and by two sub-groups: DMT-unexposed and glatiramer acetate-exposed.

Outcome frequencies will be compared with the internal comparator group and other available background prevalence from external comparator populations. The comparison of ocrelizumab-exposed women to the internal comparator will be performed using risk ratios (95% CIs) unadjusted and adjusted to relevant covariates, if sufficient number of outcomes are available. In addition to an internal comparator, existing data from external comparator populations will be used to compare the frequency of selected adverse pregnancy events and of selected adverse fetal, neonatal, and infant events at birth and through at least the first year of life of infants in the registry (where available). The Metropolitan Atlanta Congenital Defects Program (MACDP) will be the external comparator for U.S. data and EUROCAT will be the external comparator for European cases. Data collected on MS patients treated with therapies other than ocrelizumab including the Roche Multi-Source Surveillance Study of Pregnancy and Infant Outcomes in Ocrelizumab-Exposed Women with MS (protocol number: BA39732) will also be used as a comparator. These comparisons will be based on examinations of point estimates and 95% CIs from each of the sources, and no inductive statistical inferences will be made.

Interim Analyses

Interim analyses will be conducted every year provided that at least 15 new pregnancies have occurred between two interim analyses.

Milestones

Start Date of Study

The study start date will be the date of the first data collection: the date from which information on the first study patient is recorded in the study database. The anticipated start date is Q1 2019.

End of Study

The end of the study will be the date from which the last data collected from the last subject is recorded in the study database. The anticipated end of study date is October 2028.

Length of Study

This study will last approximately 10 years.

5. PROTOCOL AMENDMENTS AND UPDATES

None, as this is version 1.0 of the protocol.

6. MILESTONES

Regular study updates will be provided through periodic benefit-risk evaluation reports [PBRERs).

Study milestones are given in the following table.

Table 1 Study Milestones

Milestone	Planned Date
Registration of protocol in the E.U. PAS Register	To be determined
Start of data collection	Q1 2019
End of data collection	October 2028
Study progress reports	According to PBRER schedule
Interim analysis	Annually [a]
Final report of study results	October 2029

E.U. = European Union; PAS = post-authorization study; PBRER = periodic benefit-risk evaluation report

[a] Interim analyses will be conducted every year provided that at least 15 new pregnancies have occurred between two interim analyses.

7. RATIONALE AND BACKGROUND

7.1 STUDY RATIONALE

Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system (CNS) that affects approximately 2.3 million people worldwide (MSIF 2013). While MS is a global disease, the prevalence of MS is highest in North America and Europe (140 and 108 per 100,000, respectively) (MSIF 2013). MS is commonly diagnosed during reproductive age, between 20–40 years (Tullman 2013). Overall, women are affected approximately twice as often as men, except in individuals with the primary progressive multiple sclerosis (PPMS), where there is no gender prevalence difference (Tullman 2013; MSIF 2013). Reasons for these observed differences are unclear.

In approximately 85% of patients, MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery (relapsing remitting MS [RRMS]). If left untreated, the majority of these patients will transition to a progressive form characterized by worsening neurologic disability either with or without occasional superimposed relapses (relapsing or non-relapsing secondary progressive MS [SPMS]). Patients accumulate disability as a result of incomplete recovery from acute relapses

and/or gradual disease progression (Tullman 2013). PPMS is a less common form of MS, accounting for approximately 10% of all cases (approximately 40,000 individuals in the United States). It is characterized by a progressive course from disease onset, with infrequent superimposed discrete clinical attacks or relapses (Lublin 2014).

Evidence suggests that inflammation is present in the CNS throughout all MS clinical courses, from RRMS to SPMS and in PPMS (Frischer et al. 2009). Differences between disease phenotypes are due to the differential contribution of each of the inflammatory and neurodegenerative processes to the pathophysiology of CNS damage over time (Frischer et al. 2009; Frischer et al. 2015).

OCREVUS® (ocrelizumab) was approved by the U.S. Food and Drug Administration (FDA) on 28 March 2017, for the treatment of adult patients with relapsing forms of MS (RMS) and PPMS (Genentech Inc. 2017). Subsequently, OCREVUS was approved in the European Union (E.U.) (including Germany), Switzerland, Australia, Canada, and several other countries.

Ocrelizumab is a recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody that selectively targets CD20-expressing B cells. Two identical, randomized, active-controlled studies (OPERA I [Study WA21092] and OPERA II [Study WA21093]) have demonstrated superior efficacy outcomes versus interferon β-1a in RMS (Hauser et al. 2017); one randomized placebo-controlled study (ORATORIO [Study WA25046]) has demonstrated superior efficacy in PPMS versus placebo (Montalban et al. 2017). Results of these studies show that depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of disease, including disability progression, in addition to an impact on magnetic resonance imaging outcomes related to disease progression and reflective of neural tissue loss; thus, further supporting the hypothesis that B cells are central to the pathogenesis of both RMS and PPMS.

Ocrelizumab has demonstrated a favorable safety profile in RMS and PPMS patients (Hauser et al. 2017; Montalban et al. 2017). The proportion of patients with adverse events (AEs) was similar in ocrelizumab patients compared with interferon β-1a (both 83.3%) or placebo patients (95.1% vs. 90.0%). The proportion of patients experiencing a serious adverse event (SAE) was similar between ocrelizumab and the comparator groups (in RMS: 6.9% [ocrelizumab] and 8.7% [interferon β-1a]; in PPMS: 20.4% [ocrelizumab] and 22.2% [placebo]).

7.2 STUDY BACKGROUND

Congenital malformations, structural (e.g., cleft lip/palate, heart defects, neural tube defects, heart defects, abnormal limbs) and functional/developmental (e.g., sensory problems, metabolic disorders, nervous system problems, degenerative disorders), affect about 3.0 per 100 live births in the United States (CDC 2008) and are the leading cause of infant deaths (about 20% of all infant deaths) (Matthews et al. 2015). The

European Surveillance of Congenital Anomalies (EUROCAT) estimated the prevalence of congenital anomalies as 23.9 per 1,000 live births from 2003–2007 (Dolk et al. 2010). It is inconclusive whether MS has an impact on risk of adverse pregnancy and infant outcomes. Some studies suggest there is little evidence that MS increases the risk of adverse pregnancy, delivery, or infant outcomes including perinatal mortality, congenital malformations, and delivery complications (Mueller et al. 2002; Dahl et al. 2005; Houtchens 2007). Other studies suggest pregnancies in women with MS are associated with more frequent operative deliveries, decreased infant birth weight or infants small for gestational age compared with women without MS (Dahl et al. 2005; Dahl et al. 2008; Kelly et al. 2009).

Ocrelizumab is a humanized monoclonal antibody of an IgG1 subtype, and immunoglobulins are known to cross the placental barrier. B-cell levels in human neonates following maternal exposure to ocrelizumab have not been studied in clinical studies. There are no adequate and well-controlled data from studies in pregnant women; however transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy (Chakravarty et al. 2011; Klink et al. 2008).

It is not known whether ocrelizumab can affect pregnancy outcomes or infant outcomes in humans. However, based on pathophysiological considerations, ocrelizumab might theoretically affect pregnancy outcomes and infant outcomes in the following ways:

- By direct exposure of the fetus to ocrelizumab, which is assumed to occur after the 16th week of gestation as receptor-mediated transplacental transfer of IgG1; this is minimal during the first trimester of pregnancy (Palmeira et al. 2012; Simister 2003)
- Indirectly due to known or unknown infections or infectious complications in the mother exposed to ocrelizumab during pregnancy, which may affect the offspring, where the infection may be associated with ocrelizumab exposure
- Indirectly due to effects of ocrelizumab on the placenta

Based on the average ocrelizumab terminal half-life of 26 days reported in the studies of MS (Genentech Inc. 2017), it is expected that ocrelizumab would be eliminated from the body approximately 4.5 months after the last administration. Considering the interpatient variability (the longest terminal half-life recorded in women was 53 days) and the absence of placental transfer of immunoglobulins during the first trimester of pregnancy, it is recommended that women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab. However, women may get pregnant during this period due to noncompliance with contraception or failure of contraceptive methods.

Clinical studies of the effects on pregnancy and offspring associated with the use of ocrelizumab during pregnancy, during lactation, and/or before conception have not been performed, and experience from ocrelizumab clinical trials is limited. As of 31 January

2017, there were 25 pregnancies reported during ocrelizumab trials in MS. Seven of the 25 pregnancies were electively terminated, and no abnormalities were reported in the embryos or products of conception, one pregnancy ended in stillbirth at approximately 7-8 months of gestation, and there were two live preterm births with abnormal findings (benign nasopharyngeal neoplasm, jaundice, respiratory distress and low birth weight; temperature instability feeding difficulties, bradycardia, respiratory distress, and anemia). Eleven of the 25 pregnancies ended in a live, full-term birth and 4 pregnancies were still ongoing at the time of analysis (Vukusic et al. 2017). In an embryo-fetal development study in cynomolgus monkeys, there was no evidence of teratogenicity or embryotoxicity (Study 04-1272-1342). Also in monkeys, using doses similar to or larger than those used clinically on a mg/kg basis, increased perinatal mortality (in some cases associated with bacterial infections), depletion of circulating B cells, and toxicity to kidneys (glomerulopathy and inflammation), bone marrow (lymphoid follicle formation), and testis (reduced weight) were seen in the offspring in the absence of toxicity in the mother (Genentech Inc. 2017). Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants of women treated during pregnancy with other drugs with the same mechanism of action. Due to the potential depletion of B-cells in neonates and infants of mothers who have been exposed to OCREVUS during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B-cell levels have recovered; therefore, measuring CD19-positive B-cell level, in neonates and infants, prior to vaccination is recommended. It is recommended that all vaccinations other than live or live-attenuated should follow the local immunization schedule. Measurement of vaccine-induced response titers should be considered to check whether individuals can mount a protective immune response, because the efficacy of the vaccination may be decreased (study BN29739, unpublished results). Ocrelizumab was excreted in the milk of treated monkeys. The effects on the infant of ocrelizumab exposure through lactation are not known (Genentech Inc. 2017).

The Ocrelizumab Pregnancy Registry will be conducted to fulfill part of the FDA postmarketing requirements (PMR) (3194-3) for approval of ocrelizumab in the United States.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 RESEARCH QUESTION

To assess and characterize the frequency of maternal, fetal, and infant outcomes among women with MS exposed to ocrelizumab during the 6 months before the estimated date of conception or at any time during pregnancy.

8.2 OBJECTIVES

The objectives for this registry are as follows:

- To estimate the frequency of selected adverse pregnancy outcomes (i.e., spontaneous abortions, stillbirths, elective or therapeutic terminations, and preterm

births) in women with MS exposed to ocrelizumab during the defined exposure window

- To estimate the frequency of selected adverse fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, small for gestational age, postnatal growth and development, and outcomes related to immune suppression) at birth and through at least the first year of life of infants from pregnancies in women with MS exposed to ocrelizumab during the defined exposure window
- To compare the maternal, fetal, and infant outcomes of women with MS exposed to ocrelizumab with two unexposed control populations: one consisting of women with MS who have not been exposed to ocrelizumab before or during pregnancy and the other consisting of women without MS

9. RESEARCH METHODS

9.1 STUDY DESIGN

The design of the pregnancy exposure registry is consistent with relevant guidelines and recommendations (FDA 2002; European Medicines Agency 2005; Gliklich et al. 2014; Andrews et al. 2008). This prospective observational registry will collect primary data from 290 ocrelizumab-exposed pregnant women (153 pregnancy outcomes) with MS and their healthcare providers (HCPs) from the United States, Germany, and other potential countries (see Section 9.5). Patients who have been exposed to ocrelizumab during the 6 months prior to their last menstrual period (LMP) or at any time during pregnancy are eligible for the ocrelizumab-exposed study group. Inclusion of exposures prior to LMP is based on the half-life and standard of care infusion schedule of ocrelizumab. Dosing and treatment duration of ocrelizumab as part of this non-interventional study are at the discretion of the physician in accordance with local clinical practice and local labeling.

The internal comparator group will consist of currently pregnant women with MS who were not exposed to any MS disease-modifying therapies (DMTs) during the 6 months prior to their LMP or at any time during pregnancy (apart from glatiramer acetate [e.g., Copaxone] exposure through the first trimester (for description and rationale, see Section 9.7.2.1). Internal comparator patients will be enrolled from the same sites as the ocrelizumab-exposed women and follow the same study procedures for follow-up and data collection. Women will be eligible in the internal comparator group if they fall into one of the following categories:

- Pregnant women with MS with documentation that the patient was not exposed to any MS DMTs during the 6 months prior to their LMP or at any time during their pregnancy

  OR

- Pregnant women with MS with documentation that the patient was exposed to glatiramer acetate during the 6 months prior to their LMP through the first trimester

Major congenital malformations are the primary outcome of interest for this study, and other outcomes are classified as secondary. Data on risk factors, ocrelizumab exposure (among the exposed group), glatiramer acetate exposure (among the comparator group), other therapeutic or environmental exposures, and adverse maternal, fetal, and infant outcomes will be collected from patients and their HCPs (e.g., neurologist, obstetrician) during pregnancy and through at least 1 year after birth (infant's HCP and/or the patient). Congenital malformations will be classified according to the EUROCAT classification system.

The frequencies of outcomes will be presented in comparison to both existing databases and an internal comparator group.

The study is voluntary and exposure to ocrelizumab or glatiramer acetate (e.g., Copaxone) during the study period will be according to national labeling and local standard of care. Any currently pregnant woman with MS exposed to ocrelizumab (exposed group) or pregnant woman with MS not exposed to any MS DMTs or only exposed to glatiramer acetate, as defined above, will be eligible for the study. The total duration of participation is up to 21 months and the total expected duration of the study is approximately 10 years.

9.1.1 Registry Recruitment and Retention

Complete details of registry awareness, outreach, and retention efforts will be described in the Recruitment and Retention Plan, and may include the following methods to (1) increase awareness of the registry by using multiple approaches aimed toward HCPs and patients, such as websites, social media, print media, and scientific conferences; (2) evaluate awareness of the registry periodically; (3) accept data from multiple sources; (4) minimize the burden on HCPs; (5) ongoing communications with HCPs and patients; (6) possible compensation for HCPs; and (7) minimize the burden on subjects. Compensation will be considered for patients and/or HCPs where allowed by local regulations. All activities in this plan will be reviewed on a regular basis. The Recruitment and Retention Plan will be submitted for FDA review and approval.

9.1.1.1 Registry Awareness

The registry will utilize awareness strategies that have appeared to be effective in other pregnancy exposure registry programs. Increased awareness of the registry will use multiple approaches aimed towards both HCPs and patients, such as social media, paper and electronic media, and scientific conferences. Registry awareness activities and content will be evaluated on a regular basis to ensure target populations are being reached yet minimize any burden on the recipients. Channels for providing feedback on Registry material and corresponding with potential HCPs and patients will be detailed in the Recruitment and Retention Plan.

9.1.1.2 Outreach Efforts

Active outreach will occur to obtain reports of women with MS who are exposed to ocrelizumab during pregnancy, as well as women with MS who are eligible for the internal comparator who receive medical care from the same clinical sites. Outreach efforts may include the following:

- Discussion of the Registry with investigators participating in ocrelizumab clinical studies, with periodic written reminders
- Collaboration with investigators of independent MS pregnancy registries
- Notification of the Registry to neurologists and other practitioners who may prescribe ocrelizumab, as well as MS education and support groups, via the following:
    - E.U. Post-Authorization Study (PAS) Register
    - Ocrelizumab Pregnancy Registry website
    - Investigator awareness electronic flyer
    - Investigator referral letters
    - HCP introduction letters

Recruitment of patients is dependent on several factors: Uptake of new medications such as ocrelizumab is unpredictable and has the potential to impact the feasibility of meeting the recruitment targets in the United States and Germany. In addition, the expected pace of exposure to pregnant women and the willingness of pregnant women (both ocrelizumab-exposed and internal comparator groups) to participate in a registry are both difficult to predict. Continuous monitoring of patient recruitment (comparing projections and observed rates) will allow for strategies to be employed in response to any recruitment challenges.

9.1.1.3 Retention Efforts

Registry retention efforts will include (but not be limited to): general study eNewsletters to HCPs and an optional (opt-in) communications program that includes: engagement e-mails, SMS/e-mail/Call reminders, and thank-you messages for patients and SMS/ e-mail/call reminders for HCPs. Compensation will be issued (where allowed by local regulations) to all patients and/or HCPs who enroll in the communications program. As detailed in *FDA Guidance for Industry: Establishing Pregnancy Exposure Registries, Section IX*, study design and approach, and factors for determining if a registry should continue will be routinely evaluated (FDA 2002). The projected versus observed drop-out rates will be continuously monitored. Retention planning will be performed in advance as part of the Recruitment Risk Management with triggers for implementation of actions identified, as well as steps to take if the rate of patient completion decreases. Retention efforts for both HCPs and the patients will be documented in the Recruitment and Retention Plan. Steps to ensure recruitment and retention of patients in the Registry include actions for implementation at study start, in addition to actions that

could be implemented as the study progresses and new enrollment information becomes available.

9.1.2 Start Date of Study

The study start date will be the date of the first data collection: the date from which information on the first study patient is recorded in the study database.

9.1.3 End of Study

The end of the study will be the date from which the last data collected from the last subject is recorded in the study database. A data collection overview is provided in Appendix 2.

9.2 SETTING

HCPs who treat patients with MS including investigators involved in ongoing or future clinical studies of ocrelizumab will be informed of the study and asked to refer any patient who becomes pregnant to the appropriate study coordinating center (CC). Reporting of pregnancy exposures to ocrelizumab is voluntary and pregnancies should be reported as early as possible, ideally before prenatal testing has been performed. The same model will be used for referring and reporting pregnancies for the internal comparator group. Pregnancies with known outcomes (i.e., pregnancy loss or live birth) at the time of the initial report will not be included in the study but will be followed by Roche according to standard postmarketing pharmacovigilance.

9.2.1 Centers

This study will be conducted in Germany and the United States, and potentially in other countries. Each country will have at least one CC that is responsible for obtaining informed consent and all patient and HCP contacts during the study.

9.2.2 Study Population

Pregnant patients may be enrolled prospectively from the postmarketing setting or other clinical or observational studies of ocrelizumab. In order to reduce bias that may occur if outcome information is known prior to enrollment, women should be enrolled in the study as soon as their pregnancy is known, preferably in the first trimester.

Women who have had prenatal testing prior to enrollment that could determine the status of the fetus (e.g., amniocentesis, genetic testing, nuchal translucency screen, chorionic villus sampling, and late term ultrasound) will still be considered prospective cases. However, the primary data analysis will exclude women who have received first trimester prenatal screening, in which either aneuploid disorders or genetic disorders that cause major congenital malformations have been detected. Retrospective cases are women where the pregnancy outcome is known, prior to enrollment in the registry, either positive or negative, for major congenital malformations that are unrelated to

genetic or aneuploid disorders. Retrospective cases will be analyzed separately for both primary and secondary analysis.

No exclusion criteria will apply for this study.

9.2.2.1 Ocrelizumab-Exposed

To be eligible to participate in the ocrelizumab-exposed study group, patients must meet the following criteria prior to study entry:

- Patient consent (written or verbal per local regulations or Ethics Committee requirements) obtained prior to enrollment. If the patient is a minor, written consent must be obtained from their parent or legal guardian. Consent will be obtained in compliance with any country-specific regulations or requirements.
- Currently pregnant
- Diagnosed with MS
- Documentation that the patient was exposed to ocrelizumab at any point starting from 6 months prior to LMP
- Agrees to sign the Release of Medical Information Form permitting the study to contact her HCP(s) and the pediatric HCP for medical information
- The outcome of the pregnancy (i.e., pregnancy loss or live birth) must not be known.

9.2.2.2 Internal Comparator

To be eligible to participate in the internal comparator group, patients must meet the following criteria prior to entry:

- Patient consent (written or verbal per local regulations or Ethics Committee requirements) obtained prior to enrollment. If the patient is a minor, written consent must be obtained from their parent or legal guardian. Consent will be obtained in compliance with any country-specific regulations or requirements.
- Currently pregnant
- Diagnosed with MS
- Documentation of one of the following:
    - Pregnant women with MS who were not exposed to any DMTs during the 6 months prior to their LMP or at any time during their pregnancy
      OR
    - Pregnant women with MS who were exposed to glatiramer acetate during the 6 months prior to their LMP through the first trimester
- Agrees to sign the Release of Medical Information Form permitting the study to contact her HCP(s) and the pediatric HCP for medical information
- The outcome of the pregnancy (i.e., pregnancy loss or live birth) must not be known.

The rationale for glatiramer acetate exposure in the internal comparator is summarized in Section 9.7.2.

9.2.3 Concomitant Medication and Treatment

Concomitant medication prescribed for MS or other ongoing conditions during the observation period or introduced during the observation period will be documented in the electronic Case Report Form (eCRF) from start of therapy with ocrelizumab until discontinuation of the treatment, if applicable.

9.3 VARIABLES

9.3.1 Exposure Definition

Ocrelizumab-Exposed Group: Ocrelizumab exposure from 6 months prior to LMP through pregnancy will be recorded including dosing and dates of administration during each trimester of pregnancy.

Internal Comparator Group: The patient could be classified into one of the following categories based on MS treatment history:

- Pregnant women who were not exposed to any MS DMTs during the 6 months prior to their LMP or at any time during their pregnancy

  OR

- Pregnant women who were exposed to glatiramer acetate during the 6 months prior to their LMP through the first trimester

9.3.2 Outcome Variables

9.3.2.1 Primary Outcome

9.3.2.1.1 Congenital Malformations

Congenital malformations will be classified according to the EUROCAT classification system (see Section 9.7.2.2.1) and major congenital malformations will serve as the primary outcome in this study. The remaining outcomes described in Section 9.3.2 will be designated as secondary outcomes. All potential congenital malformations will be evaluated by a qualified, independent teratologist using all available medical records. The classification of potential congenital malformations will be based upon the teratologist's adjudication. The exact grouping of congenital malformations will mirror classification systems used in the external comparator groups.

Major congenital malformations identified up to 1 year of age by the mother or by the HCP or identified in the dysmorphological examination will be included in the primary analysis. Any defects identified after 1 year of age will be included if available, and descriptive analysis on these defects will be provided. More details will be provided in the Statistical Analysis Plan (SAP).

9.3.2.2 Secondary Outcomes

9.3.2.2.1 Elective or Therapeutic Pregnancy Terminations

Elective or therapeutic pregnancy terminations are defined as any induced or voluntary fetal loss during pregnancy. If available, data from pathologic examination of the abortus or fetus will be evaluated for structural and chromosomal defects. The reason for elective or therapeutic termination will be collected.

9.3.2.2.2 Spontaneous Abortions

A spontaneous abortion is defined as loss of a fetus due to natural causes at <20 weeks of gestation. If available, information from gross or pathologic examination of the abortus or fetus will be evaluated for structural and chromosomal defects.

9.3.2.2.3 Fetal Death or Stillbirth

Fetal death or stillbirth refers to the death of a fetus prior to birth or after 20 weeks of gestation. In the event of a stillbirth or fetal death, full pathology details will be requested and examined for structural or chromosomal defects. The final classification between fetal death/stillbirth and spontaneous abortion will be based on gestational age.

9.3.2.2.4 Live Birth

A live birth refers to a complete expulsion or extraction from its mother of a surviving neonate.

9.3.2.2.5 Preterm Birth

A live birth will be classified as preterm prior to 37 weeks of gestation (www.cdc.gov). Early preterm (<34 weeks), late preterm (34–36 weeks), early term (37–38 weeks) are additional stratifications that may be considered during the analysis and will be outlined in the SAP.

9.3.2.2.6 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 (CDC) definition (www.cdc.gov) of birth weight below the 10th percentile, between the 10th and 90th, and above the 90th percentile for age, respectively.

9.3.2.2.7 Low Birth Weight

An infant with low birth weight will be classified as weighing under 2500 g (www.cdc.gov). Very low birth weight are infants who weigh <1500 g and moderate birth weight ranges between 1500–2499 g; these are additional stratifications that may be considered during the analysis and will be outlined in the SAP.

9.3.2.2.8 Ectopic Pregnancies

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

9.3.2.2.9 Molar Pregnancies

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

9.3.2.2.10 Serious and Severe Infections and Hospitalization of Infants

A serious infection will be defined as any infection in the infant that fulfills the definition of an SAE outlined in Section 11.1.1.1. Any infant hospitalization, other than for a standard post-birth hospital stay, and severe infections of National Cancer Institute Common

Terminology Criteria for Adverse Events (NCI CTCAE) severity Grade 3, will also be captured as a secondary outcome in addition to an SAE.

9.3.2.2.11 Adverse Infant and Childhood Outcomes Related to Immune Suppression

Adverse infant and childhood outcomes related to immune suppression include neutropenia, lymphopenia, leukopenia, decreased B-cell counts, hypogammaglobulinemia, inadequate vaccine response, and events related to a potential immune mediated mechanism, including thrombocytopenia.

9.3.2.2.12 Neonatal Death

A neonatal death is defined as a death occurring in a neonate prior to 28 days of life. In the event of a neonatal death, full pathological details will be requested, and any structural or congenital defects detected will be evaluated.

9.3.2.2.13 Perinatal Death

Perinatal death is defined as the death of an infant between 28 days of life and 12 weeks of life. In the event of a perinatal death, full pathological details will be requested, and any structural or congenital defects will be evaluated.

9.3.2.2.14 Infant Death

Infant death is defined as the death of an infant occurring between 12 and 52 weeks of life. In the event of an infant death, full pathological details will be requested, and any structural or congenital defects will be evaluated.

9.3.2.2.15 Maternal Death

Maternal death is defined as the death of a pregnant woman during pregnancy, labor, or delivery. Maternal deaths for up to 12 weeks after delivery will also be reported and full pathology details will be requested.

9.3.2.3 Information Collected from Consenting Patients and Healthcare Providers

The following variables will be collected during the study, as part of the local routine clinical practice, as available:

Baseline:

- Documentation of informed consent
- Reporter of information (patient, obstetrician, neurologist)
- Patient demographics and characteristics (e.g., age of mother and father, education level, race/ethnicity, height, weight, body mass index).
- Patient, secondary contact, and HCP contact information (obstetrician, neurologist, if possible)
- Lifestyle risk factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)

- Current pregnancy information (e.g., LMP, gestational age, expected date of delivery [EDD], date and results of any prenatal tests)
- Maternal medical history:
    - Pregnancy history (e.g., parity, gravidity, previous preterm births, previous spontaneous abortions or elective or therapeutic terminations, reason for any elective or therapeutic termination, history of congenital malformations)
    - Surgical and medical history/significant maternal medications conditions other than MS (e.g., diabetes, high blood pressure)
    - MS disease history (including MS subtype and treatment history such as glatiramer acetate, disease duration, most recent Expanded Disability Status Scale [EDSS] score, if available)
    - Comorbid conditions
    - Family reproductive history (e.g., multiple births, congenital malformations, spontaneous abortions, premature births, chromosomal anomalies, developmental delays)
    - Family MS history
    - Ocrelizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable])
    - Current and prior medication use from 6 months prior to conception (including other MS treatments such as glatiramer acetate, teratogenic medications, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)

Follow-up during pregnancy (during each trimester, approximately at 14, 21, and 34 weeks gestation):

- Date of contact
- Reporter of information (patient, obstetrician, neurologist)
- Changes in contact information (maternal, secondary contact, and HCP)
- Changes in pregnancy status:
    - Gestational age
    - Any prenatal testing performed and results (e.g., rubella titer, toxoplasmosis, venereal disease research laboratory test, hepatitis screen, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein screen, glucose screen)
    - Pregnancy outcome, if applicable (e.g., elective or therapeutic termination, spontaneous abortion, ectopic pregnancy, molar pregnancy) as per Section 9.3.2

        - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
        - Autopsy results and pathology reports, if available
- Changes in MS disease status (including treatment changes and relapses, EDSS score)
- Ocrelizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable])
- Changes in comorbid conditions
- Current lifestyle factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)
- Current medications (including other MS treatments such as glatiramer acetate, teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)
- SAEs related to pregnancy (as per Section 11)

Birth outcome follow-up (approximately 4 weeks after EDD):

- Date of contact and date of pregnancy outcome or gestational age (in weeks)
- Changes in contact information; contact information for infant's HCP
- Reporter of information (patient, obstetrician, infant HCP)
- Pregnancy outcome (as per Section 9.3.2, e.g., live birth, stillbirth, spontaneous abortion, elective or therapeutic termination):
    - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
    - Autopsy results and pathology reports, if available
- Mode of birth (vaginal delivery, assisted delivery/cesarean section, type of anesthesia)
- MS disease and treatment status since last follow-up
- Ocrelizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable])
- Changes in comorbid conditions
- Current lifestyle factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)
- Current medications (including other MS treatments such as glatiramer acetate, teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)

- Infant characteristics:
    - Gestational age at birth
    - Sex
    - Weight
    - Length
    - Head circumference
    - Birth order (for multiple births), and number of fetuses
    - Laboratory values, if available (e.g., CD19, neutrophil, lymphocyte, white blood cell, immunoglobulin and platelet counts)
    - Apgar scores (1, 5, and 10 minutes)
    - Congenital malformations noted (including description and attribution)
    - Vaccination information
    - Whether infant is breastfed
- SAEs related to pregnancy (as per Section 11)
- All infant SAEs (including serious and severe infections of NCI CTCAE severity Grade 3, and hospitalizations other than for standard post-birth hospital stay)

Pediatric follow-up (approximately at 12, 26, and 52 weeks after birth):

- Reporter of information (patient, obstetrician, infant HCP)
- Infant characteristics:
    - Feeding behavior (including breastfeeding)
    - Weight
    - Length
    - Head circumference
    - Developmental milestones (e.g., social/emotional, language/communication, cognitive, movement/physical development milestones, as defined by the CDC [2016])
    - Laboratory values, if available (e.g., CD19, neutrophil, lymphocyte, white blood cell, immunoglobulin and platelet counts)
    - Evidence of any new congenital malformation since last follow-up
    - Vaccination information
    - All infant SAEs (including serious and severe infections of NCI CTCAE severity Grade 3, and hospitalizations other than for standard post-birth hospital stay)

Early termination of study participation contact, if applicable:

- Reporter of information (patient, obstetrician, infant HCP)
- Assessments appropriate for the time of withdrawal
- Reason for study withdrawal

- Ocrelizumab treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation (if applicable)
- Other medications (including other MS treatments such as glatiramer acetate, teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins and supplements, vaccinations, medications to treat other chronic diseases)
- Pregnancy status:
    - Gestational age
    - Any prenatal testing performed and results (e.g., rubella titer, toxoplasmosis, venereal disease research laboratory test, hepatitis screen, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein screen, glucose screen)
    - Pregnancy outcome, if applicable (per Section 9.3.2, e.g., elective or therapeutic termination, spontaneous abortion, ectopic pregnancy, molar pregnancy)
        - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
        - Autopsy results and pathology reports, if available
- Infant characteristics (for live births):
    - Gestational age at birth
    - Sex
    - Weight
    - Length
    - Head circumference
    - Birth order (for multiple births), and number of fetuses
    - Laboratory values, if available (e.g., CD19, neutrophil, lymphocyte, white blood cell, immunoglobulin, and platelet counts)
    - Apgar scores (1, 5, and 10 minutes)
    - Congenital malformations noted (including description and attribution)
    - Whether infant is breastfed, if applicable
- SAEs related to pregnancy, pregnancy outcomes (as per Section 11) and/or infant SAEs (including serious and severe infections of NCI CTCAE severity Grade 3, and hospitalizations other than for standard post-birth hospital stay)

Appendix 3 contains a more detailed review of data elements to be collected for this study.

9.4 DATA SOURCES

9.4.1 Collection of Data on the electronic Case Report Form

Patients' data obtained via questionnaires administered to patients or their HCPs will be recorded on eCRFs by the CC. The degree of detail and completeness of data collected is dependent on local clinical practice.

9.4.2 Data Collected during the Observation Period

After a patient provides consent, the CC will obtain demographic and contact information in addition to baseline information at the time of enrollment. All patient and HCP contact information will be confidential and will remain at the CC. The CC will then contact the patient each trimester to update contact information and ascertain the occurrence of pregnancy outcomes or other events (see Section 9.3 for list of variables). Below is a list of the expected contacts with patients and HCPs:

Expected contacts with patient:

- Enrollment
- End of Trimester 1 (approximately 14 gestational weeks)
- Mid-Trimester 2 (approximately 21 gestational weeks)
- Mid-Trimester 3 (approximately 34 gestational weeks)
- EDD plus 4 weeks
- Birth plus 12 weeks, 26 weeks, and 52 weeks (live births only)

Expected contacts with the patient's HCP (neurologist, obstetrician):

- Enrollment
- Mid-Trimester 2 (approximately 21 gestational weeks)
- EDD plus 4 weeks

Expected contacts with the infant's HCP (live births only):

- EDD plus 4 weeks
- Birth plus 12 weeks
- Birth plus 26 weeks
- Birth plus 52 weeks

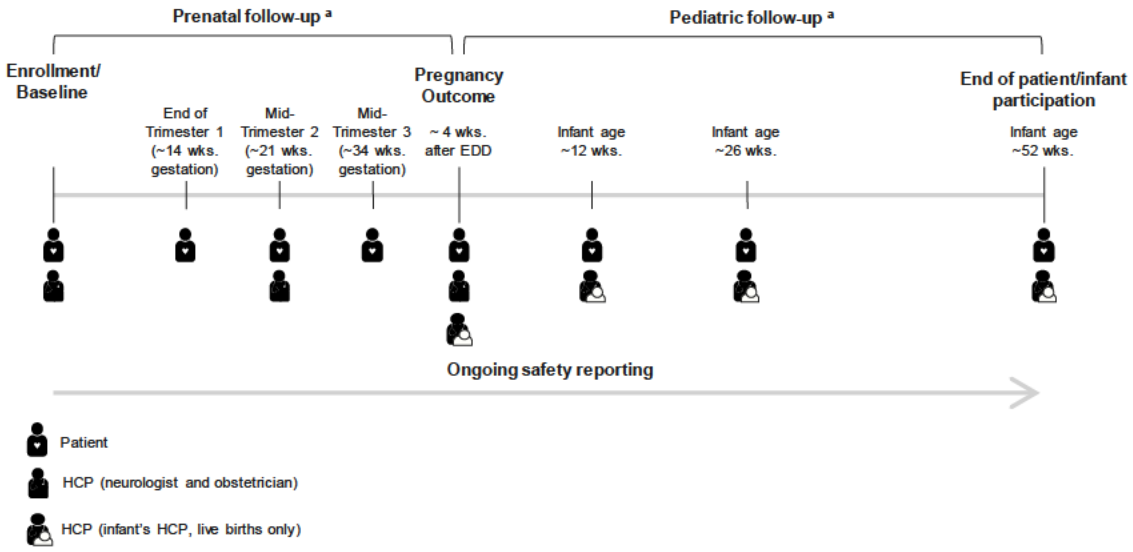
After a patient is enrolled, there will be at least three attempts made to contact the patient and/or the HCP via phone, e-mail, fax, and mail, as appropriate, approximately 10 business days apart. If data is obtained after a follow-up interval is passed, the CC will accept and enter the data and continue follow-up of the patient. If an HCP is not responsive at the time points described above, the patient will be asked to provide the information contained on the HCP worksheets. If the HCP then responds to contact, their information will supersede the patient-reported information. At all time points, the type of reporter (patient, obstetrician, neurologist, or infant HCP) will be recorded.

In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessment after treatment. Thus, no study-specific visits or evaluations are required by this protocol.

If the patient experiences an adverse pregnancy outcome or has an elective or therapeutic termination or a termination of unknown cause, the HCP and patient will be encouraged to report the outcome to the CC as soon as possible. In the event of an elective or therapeutic termination, spontaneous abortion, fetal death or stillbirth, communications with the patients will cease after pregnancy outcome information has been obtained.

See Figure 1 for data collection overview.

Figure 1 Data Collection Overview



EDD = estimated delivery date; HCP = healthcare provider (e.g., neurologist, obstetrician, infant HCP, midwife)

[a] Timepoints of patient and HCP contact shown are based on expected intervals and may vary based on real-world observational data collection

See Appendix 2 for the data collection overview (as per standard of care) during the treatment period.

9.4.3 Data Collected at Study Completion

All patients should have either the postpartum or the end of study data collection at 52 weeks postpartum (infant age 12 months), depending on the pregnancy outcome. The end of study data collection will also be completed if the patient discontinues from the study prematurely.

See Appendix 2 for the data collection overview.

9.4.4 Loss to Follow-Up

For study purposes, patients will be considered lost to follow-up if any time-based assessment is missed and the corresponding data have not been received by the CC after making additional follow-up attempts using all contact methods available (e.g., phone, fax, registered letter; see Section 9.4.2). At least three attempts will be made up to 4 months after the expected date of the missed assessment. The case will be re-opened if additional information is later obtained. All HCPs and secondary contacts will also be contacted prior to considering a patient lost to follow-up. All data collected prior to the patient being lost to follow-up will be used for analyses, if possible. For analysis purposes, the date of discontinuation will be recorded as the date of last contact.

9.4.5 Safety Data Collection

Only SAEs related to pregnancy, pregnancy outcomes, and all infant SAEs through the first year of life are required to be recorded in the eCRF during the observation period. HCPs will report SAEs related to pregnancy, pregnancy outcomes, and infants to the CC who will enter them in the eCRF. See Section 11 for a full description of safety procedures.

9.5 STUDY SIZE

The sample size for this study was calculated based on clinical, statistical, and practical considerations to determine the number of enrolled patients with pregnancies required to detect the prevalence of adverse pregnancy outcomes in the study and associated relative risk. Major congenital malformations are the primary outcome of interest for this study, and other outcomes are classified as secondary.

Assuming a 15% drop-out rate and a live birth rate of 62% (FDA 2002; Ventura et al. 2000), 290 ocrelizumab-exposed pregnant women with MS will need to be enrolled to observe 153 pregnancy outcomes. This sample size provides 80% power to detect a relative risk of 2.5 or greater in major congenital malformations relative to the baseline prevalence of 3% in the external comparator (CDC 2008) at a significance level of α=0.05 (Table 2). Should the actual live birth rate exceed 62%, fewer enrolled pregnant patients would be necessary to adequately power this study.

Table 3 shows point estimates and 95% CIs for different hypothetical numbers of observed cases. With 153 pregnancy outcomes, an observed number of 14 major congenital malformations will give an estimated prevalence of 9% with 95% CI of (5.0%-14.7%), rejecting a relative risk of 1 when the baseline prevalence is 3%. Likewise, 18 major birth defects and 46 preterm births will reject a relative risk of 1 when the baseline prevalence is 4% and 10%, respectively.

In addition to the external comparator, the internal comparator group will enroll approximately 290 pregnant women to support the study objective to compare the maternal, fetal, and infant outcomes of women with MS who have not been exposed to

ocrelizumab before or during pregnancy. The internal comparator will provide supportive evidence to the comparison with the external comparator.

Table 2 Sample Size of Pregnancy Enrollment (Outcome) for 80% Power

Relative Risks	Number of Patients Exposed to Ocrelizumab for a Single Proportion Test when Comparing with an External Comparator	Number of Patients Exposed to Ocrelizumab for a Two Proportions Test when Comparing with an Internal Comparator with a 1:1 Allocation Ratio
2.0	602 (Pregnancy outcomes needed: 317)	1489 (Pregnancy outcomes needed: 785)
2.5	290 (Pregnancy outcomes needed: 153)	793 (Pregnancy outcomes needed: 418)

Note: Sample size is calculated using 2-sided exact test at α=0.05 significance level. Sample sizes and power calculations are performed using PASS software, version 14. Assumptions: 3% baseline prevalence for major congenital malformations [a], 15% drop-out rate, 62% live birth rate [b].

[a] CDC 2008

[b] FDA 2002; Ventura et al. 2000

Table 3 95% Confidence Intervals for the Prevalence of Adverse Pregnancy Events Based on 153 Pregnancy Outcomes

Approximate Number of Adverse Pregnancy Events (Prevalence of Events) [95% Exact 2-Sided Clopper-Pearson Confidence Interval]		
3% (Major Congenital Malformations) [a]	4% (Major Birth Defects in Ocrelizumab-Exposed Patients) [b]	10% (Preterm Births) [c]
5 (3%) [0.9%, 7.1%]	6 (4%) [1.5%, 8.4%]	15 (10%) [5.7%, 15.9%]
9 (6%) [2.8%, 11.0%]	12 (8%) [4.2%, 13.5%]	31 (20%) [14.0%, 27.2%]
14 (9%) [5.0%, 14.7%]	18 (12%) [7.3%, 18.2%]	46 (30%) [22.9%, 37.9%]

[a] CDC 2008

[b] Ocrelizumab Investigator's Brochure 2016

[c] Ferré et al. 2016

9.6 DATA MANAGEMENT

9.6.1 Data Quality Assurance

[redacted], the contract research organization (CRO), will be responsible for data management of this study, including quality checking of the accuracy, completeness and timeliness of data recorded. Data submitted to the CC manually will be entered into the electronic data capture (EDC) system. CCs will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification

from the CCs, which the CCs will resolve by providing answers to the data queries electronically in the EDC system.

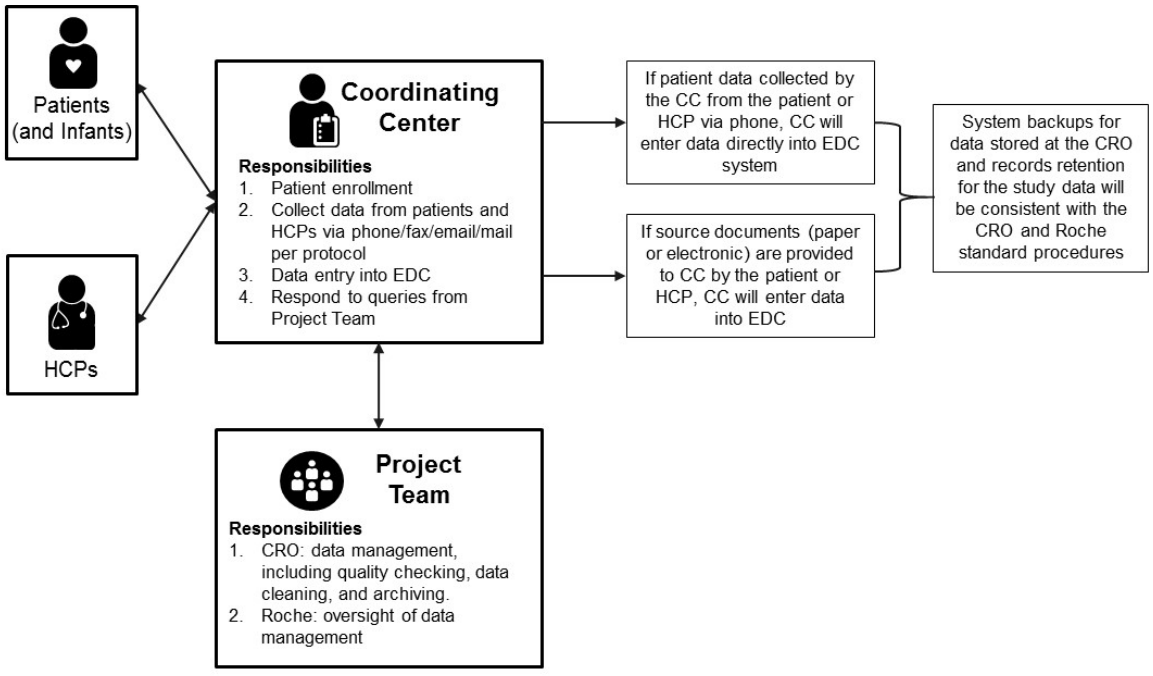
The CRO will produce a Data Quality Review Plan that describes the quality checking to be performed on the data.

Roche will perform oversight of the data management of this study, including approval of the CRO data management plans (including Data Quality Review Plan) and guidance.

eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO standard procedures. The CRO will comply with Roche's procedures regarding archiving and record management.

See Figure 2 for data flow overview.

Figure 2 Data Flow Overview



CC = coordinating center; CRO = contract research organization; EDC = electronic data capture; HCP = healthcare provider (e.g., neurologist, obstetrician, infant HCP, midwife)

9.6.2 Electronic Case Report Forms

The CRO will be responsible for designing the eCRFs with input and final approval from the Roche. eCRFs are to be completed using the EDC system. CCs will receive training and have access to a manual for appropriate eCRF completion.

All eCRFs should be completed by designated, trained CC staff. eCRFs should be reviewed and electronically signed and dated by the CC investigator.

At the end of the study, the CC investigator will receive the data related to patients from his or her CC in an electronically readable format (e.g., on a compact disc). Data must be kept with the study records. Acknowledgement of receipt of the data is required.

9.6.3 Source Data Documentation

Roche or designee representatives may conduct onsite source data verification (SDV) visits as defined in the Study Monitoring Plan at the study facilities for the purpose of monitoring various aspects of the study. Roche or designee representatives may confirm that critical protocol data (i.e., source data) entered in the eCRF by authorized CC personnel into the EDC are accurate, complete, and verifiable from source documents (e.g., questionnaires).

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time.

Before study initiation, the types of source documents that contain study-relevant information will be clearly defined in the Study Monitoring Plan. The Study Monitoring Plan defines which kind of source data – if available from clinical routine – can be used for documentation into an eCRF.

Source documents that are required to verify the validity and completeness of data entered in the eCRF must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 9.8.3.

To facilitate SDV, the CC investigators must provide direct access to applicable source documents and reports for study-related monitoring, Roche audits, and Institutional Review Board/independent Ethics Committee (IRB/IEC) review. The participating CCs must also allow inspection by applicable health authorities.

9.7 DATA ANALYSIS

Descriptive statistics will be used to summarize the findings; specifically, overall frequency (prevalence, 95% CI) of selected adverse pregnancy outcomes will be calculated, as well as frequencies of specific outcomes, e.g., major congenital malformations (primary outcomes); spontaneous abortions, stillbirths, elective or therapeutic terminations, and preterm births (secondary outcomes). Prevalence and associated 95% CIs will also be calculated for selected adverse fetal, neonatal, and infant outcomes at birth and through at least the first year of life of infants from pregnancies in women with MS exposed to ocrelizumab (i.e., major and minor congenital malformations, small for gestational age, postnatal growth and development, and outcomes related to immune suppression. Similar descriptive analyses summarized above will be performed on the internal comparator group consisting of pregnant women with MS who were not exposed to any MS DMTs (apart from glatiramer acetate). Outcomes will be compared with the internal comparator group and other available

background prevalence from external comparator populations. See Methods of Analysis Section 9.7.1 for additional details.

The comparison to ocrelizumab-exposed women to the internal comparator will be performed using risk ratios (95% CIs) unadjusted and adjusted to relevant covariates, if sufficient number of outcomes are available. See Comparative Analysis Section 9.7.2 for additional details.

All patients enrolled meeting the eligibility criteria will be included in the analytic population. All analyses will be conducted on an overall basis, by earliest trimester of ocrelizumab exposure, as well as presented by enrollment type (i.e., prospective versus retrospective; see Section 9.2.2). The primary analysis will exclude women who have received first trimester prenatal screening in which either aneuploid disorders or genetic disorders that cause major congenital malformations have been detected. A sensitivity analysis of major congenital malformations will exclude women exposed to any known teratogenic medications during pregnancy. If sufficient numbers are obtained, analyses will also be presented according to maternal age, race/ethnicity, gestational age at enrollment, elective or therapeutic pregnancy termination status, prenatal screening result (positive versus negative), glatiramer acetate exposure (internal comparator group), and other important risk factors. Prevalence and associated 95% CIs will be calculated.

9.7.1 Methods of Analysis

Demographic information (e.g., age, race/ethnicity, body mass index [BMI]), clinical characteristics, and other potential factors that may affect pregnancy outcome will be described. Descriptive statistics (i.e., mean, SD, median, minimum, and maximum) will be provided for continuous variables. Counts and percentages will be provided for categorical variables. The number of patients with non-missing data will be presented.

Prenatal exposure to ocrelizumab will be summarized based on the timing of exposure by trimester. Total duration of exposure will be calculated using the start date of ocrelizumab use and the stop date +6 months.

The prevalence of spontaneous abortions will be calculated by dividing the number of fetal losses occurring before 20 weeks gestation by the total number of pregnancies. Spontaneous abortions defined as occurring before 22 weeks gestation will also be examined in a sensitivity analysis to account for global variation in the definition for this outcome. Prevalence per 100 pregnancies along with 95% CIs will be presented.

The prevalence of congenital malformations will be calculated using Metropolitan Atlanta Congenital Defects Program (MACDP) and EUROCAT conventions. The total prevalence will be calculated by dividing the number of cases of each event (observed in live births, fetal deaths, elective or therapeutic terminations, and at any gestational age) by the total number of births (stillbirths + live births). The prevalence *at birth* will be

calculated as number of cases observed in live births and stillbirths divided by the total number of births (stillbirths + live births). Prevalence per 100 births along with 95% CIs will be presented.

Prevalence of preterm birth and small for gestational age will be calculated by dividing the number of cases by the total number of births (stillbirths + live births). Prevalence per 100 births and corresponding 95% CIs will be presented.

For growth and developmental delays, the prevalence will be calculated as the number of cases divided by the total number of live births. Prevalence per 100 live births and 95% CIs will be calculated.

Exact 95% CIs including Clopper-Pearson CI for binomial proportion will be assessed.

Exploratory analyses will be conducted to study the effects of the timing of ocrelizumab exposure before and during pregnancy and cumulative exposure periods on each outcome. Full details on exploratory analyses will be described in the SAP.

The analyses summarized in this Section will also be performed on the internal comparator group consisting of pregnant women with MS who were not exposed to any MS DMTs (apart from glatiramer acetate). The internal comparator group will be analyzed overall (all eligible internal comparator pregnancies) and by two sub-groups: MS DMT-unexposed and glatiramer acetate-exposed.

Full details of the statistical analyses will be provided in the SAP.

9.7.2 Comparative Analyses

Congenital malformation reporting rates, spontaneous abortion rates, and preterm birth rates from the study will be compared with the internal comparator group and other available background rates from external comparator populations including, but not limited to: EUROCAT, MACDP, and the Roche Multi-Source Surveillance Study of Pregnancy and Infant Outcomes in Ocrelizumab-Exposed Women with MS (protocol number: BA39732). These comparisons will be based on examination of point estimates and 95% CIs from each of the sources and in order to facilitate comparisons, details regarding the coding classification and case definition will be made as similar as possible. Details about how to set coding and classification of each event comparable to each external data source will be described in the SAP.

For the internal comparison group, methods such as causal inference models using baseline characteristics will be outlined in the SAP. The comparison of the internal comparator to ocrelizumab-exposed women will be performed using risk ratios (95% CIs) unadjusted and adjusted to relevant covariates, if sufficient number of outcomes are available.

9.7.2.1 Internal Comparator Group

The internal comparator group will consist of pregnant women with MS who are unexposed to DMTs, apart from glatiramer acetate (See Section 9.2.2.2). Identical data collection and follow-up procedures will be used for the ocrelizumab-exposed pregnant women and unexposed pregnant women with MS. Covariates collected in both exposed and unexposed groups include the following: pregnancy follow-up and frequency of mother and infant encounters, medical and medication history, MS disease history and relapses during follow-up, and pregnancy and infant outcomes (see Appendix 2 and 3). This comparator study population will be recruited from the same clinical centers as the ocrelizumab-exposed pregnant women, in both the United States and other countries.

There is sufficient clinical evidence to allow pregnant women with MS who are exposed to glatiramer acetate early in pregnancy to enroll in the internal comparator. Since FDA drug approval in 1996, studies of glatiramer acetate have not shown to increase the risk of adverse pregnancy or delivery outcomes compared to women unexposed to DMTs during pregnancy (Copaxone [Teva] Prescribing Information; Fragoso 2014; Sandberg-Wollheim et al. 2018), including in the first trimester (Herbstritt et al. 2016); thus, exposure to this particular MS DMT will be permitted as part of the ocrelizumab-unexposed group to increase the feasibility to recruit and internal comparator group from the same sites. However, analyses stratification based on glatiramer acetate exposure will also be performed.

9.7.2.2 External Comparators

9.7.2.2.1 European Surveillance of Congenital Anomalies (EUROCAT)

EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies (EUROCAT 2017). Started in 1979, the registry includes over 1.7 million births surveyed annually in Europe from 43 registries in 23 countries. Approximately 29% of the European birth population is covered by this network. These population-based registries facilitate the early warning of new teratogenic exposures, evaluate the effectiveness of primary prevention measures, and assess the impact of developments in prenatal screening.

Using 13 registries from the EUROCAT network from 1 January 1998 through December 31, 2011, Groen et al. reported an overall prevalence of congenital anomaly of 27.3 per 1000 births (range, 19.1–39.3 per 1000 births) (Groen et al. 2017). Of the 84,387 pregnancies with a known outcome (99.4%), 2.33% pregnancies were stillbirths, the proportion of early neonatal mortality (within 7 days of birth) was 2.37% and the proportion of late neonatal mortality (between 7-27 days of life) was 0.84%.

9.7.2.2.2 Metropolitan Atlanta Congenital Defects Program (MACDP)

The MACDP, a population-based tracking system for birth defects, was established in 1967 as the first population-based system for the active collection of information about birth defects in the United States (MACDP 2016). Currently, the MACDP tracking system captures approximately 35,000 births per year from three large metropolitan

counties in the Atlanta area (five counties were captured in earlier years). MACDP has monitored trends in birth defects rates and has served as a case registry for descriptive, risk factor, and prognostic studies of birth defects. Since 1998, MACDP surveillance has required that any signs or symptoms of a defect in the child be reported before their sixth birthday. In a 2007 report, the MACDP presented data on the prevalence and descriptive characteristics of birth defects, including 67 individual defects, in metropolitan Atlanta, Georgia, from 1968–2003 (Correa et al. 2007).

The frequency of birth defects is measured as prevalence at birth, expressed as the number of affected infants per 1,000 live births. Major structural or genetic birth defects affected approximately 3% of births in the United States (CDC 2008). The prevalence estimates of stillbirth in 2006 and 2008 using MACDP data were 8.0 and 7.6 per 1000 live births plus stillbirths (95% CIs: 7.3, 8.7 and 6.9, 8.4), respectively (Duke and Gilboa 2014).

9.7.2.2.3 Roche Multi-Source Surveillance Study of Pregnancy and Infant Outcomes in Ocrelizumab-Exposed Women with MS (BA39372)

The Roche Multi-Source Surveillance Study of Pregnancy and Infant Outcomes in Ocrelizumab-Exposed Women with MS is a non-interventional multi-database postmarketing safety study to assess pregnancy-related safety data from women with MS exposed to ocrelizumab. Utilizing secondary data sources from the United States and Denmark, this matched cohort study will use multiple sources of previously collected data to assess and characterize pregnancy and infant outcomes of women with MS exposed to ocrelizumab during the 6 months before the estimated date of conception or at any time during pregnancy. Mother-child linked data will be extracted from existing health care claims databases in the United States and population-based patient registries in Denmark.

Given that pregnancy registries can be subject to low enrollment, the use of this real-world data source in the same or similar countries with regards to underlying MS incidence provides a suitable comparator of pregnancy and infant outcomes among women with MS who are exposed and unexposed to ocrelizumab. Any patterns or suspected biases can be examined and compared in this data resource and the Ocrelizumab Pregnancy Registry outlined in this protocol.

9.7.3 Interim Safety Analyses and Timing of Analyses

Interim analyses will be conducted every year provided that at least 15 new pregnancies have occurred between two interim analyses.

9.8 QUALITY CONTROL

9.8.1 Study Documentation

The CC must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol

amendments, Informed Consent Forms (ICFs), and documentation of IRB/IEC and governmental notification. In addition, at the end of the study, the physician will receive the patient data, which include an audit trail containing a complete record of all changes to data.

Roche shall ensure that the dataset and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

9.8.2 Coordinating Center Audits and Inspections

CC visits may be conducted by Roche or an authorized representative for audit of study data, patients' medical records, and eCRFs.

The investigator will also permit national and local health authorities to inspect facilities and records relevant to this study.

9.8.3 Retention of Records

Records and documents pertaining to the conduct of this study, including eCRFs and ICFs, must be retained by the CC for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of Roche. Written notification should be provided to Roche prior to transferring any records to another party or moving them to another location.

All supporting functional parties will comply with Roche procedures regarding archiving and record management.

9.8.4 Administrative Structure

9.8.4.1 External Advisors

A qualified independent teratologist or other appropriate birth defect expert will be used throughout the study for evaluation of congenital malformations and other significant findings. Other experts in relevant specialties will also be consulted by the Sponsor as deemed necessary by the external advisors.

9.9 LIMITATIONS OF THE RESEARCH METHOD

Although all possible measures will be taken to ensure the quality and robustness of the data, there are several limitations inherent to the study design that should be acknowledged.

Spontaneous abortions most frequently occur in early pregnancy, likely before the pregnancy is recognized. Even if the pregnancy is recognized and confirmed, it is

possible that the pregnancy may not be reported to the study if the loss occurred before enrollment into the study. Not capturing all early pregnancy losses will likely lead to an underestimation of the true early pregnancy loss rate. There is no reason to believe that this study will be differentially impacted by this bias so even though the spontaneous early losses may be underestimated, the relative rate compared with the other registries should not be affected.

Reporting outcomes in this study is voluntary and it is possible that not all patients will complete all of the follow-up assessments. If data from a patient and their HCPs is unattainable, the patient will be considered lost to follow-up. It is possible that the outcomes from pregnancies lost to follow-up could differ from those with documented outcomes. Comparisons of the characteristics of patients with completed information and those lost to follow-up will be conducted in an attempt to address this potential bias.

This study plans to enroll both retrospective patients (women where the pregnancy outcome is known, prior to enrollment in the registry, either positive or negative, for major congenital malformations that are unrelated to genetic or aneuploid disorders), and prospective patients (women where the pregnancy outcome is unknown prior to enrollment in the registry, or pre-enrollment prenatal screening for congenital malformations that are unrelated to genetic or aneuploid disorders was not performed). Patients who have been informed about a potential adverse pregnancy outcome prior to enrollment in the study may differentially recall their exposures during early pregnancy and may also have changed their exposures after learning of the outcome. The differential recall may lead to bias, which we will attempt to address with the stratification of primary and secondary outcomes by retrospective and prospective status.

As noted in Section 9.1, there is potential for channeling bias by label indication due to the severity of MS at baseline and patient relapse history. Women with more severe MS may be indicated for ocrelizumab use compared with women who have less severe MS. Baseline severity of MS will be captured to assess the degree of confounding by indication.

10. PROTECTION OF HUMAN SUBJECTS

10.1 PATIENT DISCONTINUATION

Patients have the right at any time and for any reason to withdraw their consent that their data are collected and used for the study. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Patient death
- Patient lost to follow-up

10.1.1 Discontinuation from Treatment with Studied Medicinal Products

The decision for discontinuation from treatment lies with the treating physician in agreement with the patient's decision and is not regulated by this protocol.

10.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF page. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

10.1.3 Study and Coordinating Center Discontinuation

Roche has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Patient enrollment is unsatisfactory
- Patient safety

Roche will notify the physician if the study is placed on hold, or if they decide to discontinue the study.

Roche has the right to replace a CC at any time. Reasons for replacing a CC may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) or any other pertinent local law or guideline

10.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research is conducted.

The study will comply with national and E.U. requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

10.3 INFORMED CONSENT

Roche's sample ICF (ICF and ancillary sample ICFs such as Caregiver's ICF, health status data release form [maternal and infant], if applicable) will be provided to each CC. If applicable, it will be provided in a certified translation of the local language. Roche must review and approve any proposed deviations from Roche's sample ICFs or any

alternate ICFs proposed by the CC (collectively, the “Consent Forms”) before IRB/IEC submission. The final Consent Forms approved by the IRB/IEC must be provided to Roche for health authority submission purposes according to local requirements.

The patient consent (written or verbal per local regulations) must be obtained from the patient or the patient’s legally authorized representative before start of documentation of his or her data in the eCRF. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to first documentation of this patient’s data in the eCRF.

For the purposes of follow-up with the infant’s HCP, the patient will be expected to provide proxy informed consent on behalf of the infant. Where possible, this proxy consent will be included in the patient’s informed consent signed at enrollment. Otherwise, prior to the collection and entry of postpartum and through at least 1 year follow-up data, the physician will be required to obtain informed consent from the patient on behalf of the infant (where required, consent of both parents will be sought). Study staff from the CRO will provide reminders to physicians at appropriate time points to ensure the proxy infant consent is obtained.

By signing the ICF, the patient confirms that he/she has been informed about the study and agrees to pseudonymous data collection, pooling of data with similar scientific data, and the possibility of monitoring activities. It is the responsibility of the physician to obtain written informed consent from each patient participating in the study either in person or remotely, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The physician must also explain that the patient is completely free to refuse to enter the study or to withdraw from it at any time, for any reason and without losing the benefit of any medical care to which the patient is entitled or is presently receiving.

A copy of each signed ICF must be provided to the patient or the patient’s legally authorized representative. All signed and dated ICFs must remain in each patient’s study file or in the site file and must be available for verification by Site Operations Representative at any time.

For CCs in the United States, each ICF may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the CC utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply, except that IRB review and approval may not be required per study CC policies.

10.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/IEC by the Site Operations Representative in consultation with the Scientific Responsible and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC.

In addition to the requirements for collecting and reporting all AEs and SAEs to Roche, physicians must comply with requirements for AE reporting to the local health authority and IRB/IEC.

10.5 CONFIDENTIALITY

Confidentiality standards will be maintained by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any Roche location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Roche monitors, representatives, and collaborators, and the IRB/IEC for each CC, as appropriate.

By signing the protocol, the participating physician commits to complying with all related applicable local laws and regulations, including but not limited to the regulations in 45 CFR parts 160 and 164 (protected health information), such regulations also known as the "HIPAA Privacy Regulations" and the Data Privacy Act.

10.6 FINANCIAL DISCLOSURE

Physicians will provide Roche with sufficient, accurate financial information in accordance with local regulations to allow Roche to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Physicians are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient's last assessment).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

Product-specific pregnancy registries often fail to provide clinically meaningful information because of inadequate enrollment. Enrollment in registries may be low, as HCPs may not have sufficient time to spend time with patients discussing the registry, enroll patients, and complete Case Report Forms or send medical records (FDA 2014).

Therefore, in order to balance successful registry data collection requirements to fulfill the study objectives and to minimize the administrative burden for HCPs, only pregnancy outcome-related SAEs and infant SAEs will be collected in this study, in addition to the following AEs (including non-serious events) reported in neonates and infants: severe infections (NCI CTCAE Grade 3, 4 and 5) and adverse infant and childhood outcomes related to immune suppression (including neutropenia, leukopenia, lymphopenia, decreased B-cell counts, hypogammaglobulinemia, and inadequate vaccine response) as well as thrombocytopenia. Other AEs, including SAEs, not related to pregnancy outcomes, will not be collected in this registry. These AEs/SAEs must be reported to Roche Safety via the pharmacovigilance system, as for any spontaneous reporting of AEs for ocrelizumab events, and to the MAH for glatiramer acetate events. Relevant contact details pertaining to spontaneous safety reporting are mentioned in the ocrelizumab or glatiramer acetate local product label.

11.1 SAFETY REPORTING REQUIREMENTS FOR STUDIED MEDICINAL PRODUCTS

11.1.1 Safety Parameters and Definitions

The reporting requirements in this section apply to all studied medicinal products (observational products of interest, as specifically stated in the study objectives).

Safety assessments will consist of monitoring and recording SAEs related to pregnancy, pregnancy outcomes, and any infant SAEs for the first year of life (e.g., serious infections, severe infections of NCI CTCAE severity Grade 3, and any infant hospitalization, other than for a standard post-birth hospital stay). In order to evaluate adverse outcomes possibly related to immune suppression/immune mediated mechanism, the following serious and non-serious events will be collected in neonates and infants until 1 year of age: neutropenia, lymphopenia, leukopenia, decreased B-cell counts, hypogammaglobulinemia, and inadequate vaccine response (including low vaccine-induced response titers) as well as thrombocytopenia, if possible.

11.1.1.1 Assessment of Serious Adverse Events (Immediately Reportable to the Roche)

Serious Adverse Events

Only pregnancy-related SAEs, pregnancy outcomes, and infant SAEs will be collected in this study.

An SAE is any untoward medical occurrence that:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient’s ability to conduct normal life functions)
- Is a significant medical event in the physician’s judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

Obstetric complications that fall into the above categories are defined as pregnancy-related SAEs in this study and should be reported to the CC.

A pregnancy outcome is as outlined in Section 9.3, Outcome Variables, and covers:

- Spontaneous abortion
- Fetal loss including stillbirth
- Ectopic pregnancy
- Molar pregnancy
- Congenital malformation
- Elective or therapeutic pregnancy terminations
- Premature birth

The reporting HCP must assess the relationship to the studied medicinal product and severity for each SAE recorded on the eCRF (see Appendix 4).

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to the NCI CTCAE; see Appendix 4).

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

Non-Serious Adverse Events

In neonates and infants, the following non-serious AEs will be collected during their first year of life: severe infections of NCI CTCAE severity Grade 3, neutropenia, lymphopenia, leukopenia, thrombocytopenia, decreased B-cell counts, hypogammaglobulinemia, and

inadequate vaccine response, including low vaccine-induced response titers (for laboratory test results see also Appendix 4.3.3).

Other non-serious AEs and any other safety information not falling under the definitions above will not be collected as part of the study database. All non-pregnancy related SAEs and AEs for patients enrolled in the study and receiving ocrelizumab (i.e., "studied medication") **must** be reported to Roche Safety department to be processed following standard pharmacovigilance practices, and to the MAH for glatiramer acetate events. Relevant contact details pertaining to spontaneous safety reporting are mentioned in the local product label.

11.1.2 Methods and Timing for Capturing and Assessing Safety Parameters

The CC is responsible for ensuring that all SAEs related to pregnancy, pregnancy outcomes, and infants, as well as the following non-serious AEs during the neonate's/infant's first year of life: severe infections of NCI CTCAE severity Grade 3, neutropenia, lymphopenia, leukopenia, thrombocytopenia, decreased B-cell counts, hypogammaglobulinemia, and inadequate vaccine response, including low vaccine-induced response titers, are reported by HCPs as per protocol (see Section 11.1.1.1 for definition) and are recorded in the eCRF.

Once the patient is enrolled in the study, SAEs related to pregnancy will be collected until the end of her observation period, i.e. until a pregnancy outcome is reported, unless the patient withdraws from the study prematurely. SAEs and the selected non-serious AEs described above experienced by the infant will be reported until the first year of life.

11.1.2.1 Serious Adverse Event Reporting Period

The CC will seek information on pregnancy related SAEs at each patient and HCP contact. All SAEs related to pregnancy, pregnancy outcomes, and infants, whether reported by the patient or by HCPs, will be recorded in the SAE section of the eCRF.

11.1.2.2 Procedures for Recording Serious Adverse Events

HCPs should use correct medical terminology/concepts when reporting SAEs related to pregnancy and pregnancy outcomes to the CC. Colloquialisms and abbreviations should be avoided.

Only one SAE term should be recorded in the event field of the eCRF.

11.1.3 Reporting Requirements from Physician to Marketing Authorization Holder

11.1.3.1 Immediate Reporting Requirements from Physician to Marketing Authorization Holder

SAEs require immediate reporting to allow Roche and the regulatory authorities to take appropriate measures to address potential new risks associated with the use of the

medicine. The physician must report such events to Roche immediately; under no circumstances should reporting take place more than 24 hours after the physician learns of the event.

If an HCP or a patient reports any non-pregnancy-related SAEs, these SAEs must be forwarded to Roche to process as a spontaneous report for ocrelizumab events and the MAH for glatiramer acetate events. (Refer to local product label for relevant contact details).

The CC will consult with Roche for questions regarding whether an SAE falls into the definition of a pregnancy-related SAE as per Section 11.1.1.1 (i.e., any obstetric complication fulfilling one of the criteria for a SAE).

11.1.3.2 Reporting Requirements for Non-Serious Adverse Events

Selected non-serious AEs will be collected as part of the study database (see Section 11.1.1 and Appendix 4.3.3). If an HCP or a patient reports any non-pregnancy-related AEs, these AEs must be forwarded to Roche to process as a spontaneous report for ocrelizumab events and the MAH for glatiramer acetate events (refer to local product label for relevant contact details).

11.1.3.3 If EDC System is Temporarily Unavailable

In the event that the EDC system is temporarily unavailable, a completed paper reporting form and fax coversheet should be faxed/scanned to Roche Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the SAE), using the fax number or e-mail address provided.

Once the system is available again, all information should additionally be entered and submitted via the EDC system.

11.1.4 Follow-Up of Patients after Pregnancy Related Adverse Events

11.1.4.1 Physician Follow-Up

The physician should follow each SAE related to pregnancy until the event has resolved to baseline grade or better, the event is assessed as stable by the physician, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs related to pregnancy considered to be related to ocrelizumab for all relevant information and until a final outcome can be reported.

During the study period, resolution of SAEs related to pregnancy (with dates) should be documented in the SAE section of the eCRF.

11.1.4.2 Marketing Authorization Holder Follow-Up

For all SAEs related to pregnancy, Roche or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

12. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of the study, Roche is dedicated to openly providing information on the study to HCPs and to the public, both at scientific congresses and in peer-reviewed journals. Roche will comply with all requirements for publication of study results and will submit all study reports to the health authorities through scheduled PBRERs.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to Roche prior to submission for publication or presentation. This allows Roche to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating physician will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate Roche personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Roche plans to publish the design of the pregnancy registry, interim results, and final results.

13. REFERENCES

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Appendix 1
ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 section number 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). 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).

Study title:
OCRELIZUMAB PREGNANCY REGISTRY

Study reference number:
WA40063

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☒*	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

*Registration in the EU PAS register will occur after the FDA approved protocol is registered on ClinicalTrials.gov.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1

[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 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.5
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.5
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.1
	4.2.2 Age and sex?	☒	☐	☐	9.2.2
	4.2.3 Country of origin?	☒	☐	☐	9.1
	4.2.4 Disease/indication?	☒	☐	☐	9.1, 9.2.2
	4.2.5 Duration of follow-up?	☒	☐	☐	9.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.1, 9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.1, 9.3.1

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.6.1
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.1, 9.9
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.2.2
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
	9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7.2
	9.3.3 Covariates?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6.1, 9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6.1, 9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8.4.1

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.2.2
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.1.1, 9.5

Comments:

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.4
13.3 Have data protection requirements been described?	☒	☐	☐	10.5

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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

Date: 23 September 2018

Signature: [redacted]

Appendix 2
Data Collection Overview (as per Standard of Care)

Data Collection [a]	Enrollment	Prenatal Follow-Up			Pregnancy Outcome	Pediatric Follow-Up	Early Termination of Study Participation Contact
		End 1st Trimester (~14 weeks)	Mid 2nd Trimester (~21 weeks)	Mid 3rd Trimester (~34 weeks)	~4 weeks after EDD	Infant Age 12, 26, and 52 Weeks	End of Patient Participation in Study
Informed consent [b]	x						
Inclusion/exclusion criteria	x						
Patient demographics and characteristics	x						
Medical history	x						
MS disease and treatment history	x						
Pregnancy history, and current pregnancy information [c]	x						
Lifestyle factors [d]	x	x	x	x	x		
Prior and concomitant medications [e]	x	x	x	x	x		
Ocrelizumab treatment [f]	x	x	x	x	x		x
Comorbid conditions	x	x	x	x	x		
MS disease status [g]		x	x	x	x		
Current pregnancy status		x	x	x			x [h]
Gestational age (weeks)		x	x	x	x		x [h]
Pregnancy outcome [i]					x		x [h]
Infant characteristics					x [j]	x [k]	x [h]
Infant abnormalities [l]					x	x	x [h]
SAEs related to pregnancy,	x	x	x	x	x	x	x [h]

Data Collection [a]	Enrollment	Prenatal Follow-Up			Pregnancy Outcome	Pediatric Follow-Up	Early Termination of Study Participation Contact
		End 1st Trimester (~14 weeks)	Mid 2nd Trimester (~21 weeks)	Mid 3rd Trimester (~34 weeks)	~4 weeks after EDD	Infant Age 12, 26, and 52 Weeks	End of Patient Participation in Study
pregnancy outcome, or infant SAEs and severe infections (NCI CTCAE Grade 3) in infants [m]							
Reason for early termination of study participation							x

EDD = expected date of delivery; EDSS = Expanded Disability Status Scale; LMP = last menstrual period; MS = multiple sclerosis; SAE = serious adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

[a] Available data will be collected; no additional diagnostic or monitoring procedures shall be applied to the patients outside of routine clinical practice.

[b] Written or verbal informed consent must be obtained before any data collection (per local regulations or ethics committee requirements). If the patient is a minor, written consent must be obtained from the parent or legal guardian.

[c] Including previous pregnancy outcomes, detailed family history including pregnancy complications, adverse pregnancy outcomes and developmental abnormalities, and information about baseline risks.

[d] Including smoking, use of caffeine, use of alcohol, and use of recreational drugs.

[e] Prior and concomitant medications up to 6 months prior to LMP.

[f] Start and stop dates, dose, dosing frequency, reason for discontinuation (if applicable)

[g] MS disease status and MS relapses since enrollment including EDSS, if available

[h] If applicable

[i] Including live births, spontaneous abortions, stillbirths, elective or therapeutic terminations, reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), and autopsy results and pathology reports, if available

[j] Gestational age, sex, weight, length, birth order (for multiple births), Apgar scores, breastfeeding status, and any congenital malformation noted, including description and attribution.

[k] Including postnatal growth and development: feeding behavior, weight, length, developmental milestones, breastfeeding status, evidence of any abnormality, and outcomes possibly related to immune suppression/immune mediated mechanism (neutropenia, lymphopenia, leukopenia, decreased B-cell counts, hypogammaglobulinemia, inadequate vaccine response [including low vaccine-induced response titers] and thrombocytopenia), if applicable.

[l] Detailed information on any infant abnormalities identified after infant birth.

[m] Reported throughout the study or until study discontinuation as applicable

Appendix 3
Collection of Data Elements

Variables

The tables below further characterize variables corresponding data elements that will be collected during the study, as part of the local routine clinical practice, as available. Variables and variable specifications are subject to change.

Table 1. Baseline

Variable Category	Data Elements	Additional Information
Country of Study	United States, Germany	Other, If applicable
Reporter of Information	Patient	Contact information; Secondary contact (if available)
	Obstetrician	Contact information
	Neurologist	Contact information
	Other (please specify)	Contact information
Eligibility	Informed consent collected from the patient and partner (if applicable)	Date of informed consent also collected
	Prior to the time of enrollment, has there been any result from maternal health screening tests that was indicative of a negative pregnancy outcome (e.g., toxoplasmosis screen and syphilis [Venereal Disease Research Laboratory, Rapid Plasma Reagin] blood screen)?	
	Prior to the time of enrollment, has any prenatal testing (e.g., amniocentesis, genetic testing, nuchal translucency screen, chorionic villus sampling, and late term ultrasound) been carried out that provides knowledge of the pregnancy outcome?	
	Currently pregnant	
	Diagnosed with MS	
	Ocrelizumab-exposed group: Documentation that the patient was exposed to ocrelizumab at any point starting	

Variable Category	Data Elements	Additional Information
	from 6 months prior to LMP	
	Internal comparator group: Documentation that the patient was not exposed to any DMT (apart from glatiramer acetate exposure) at any point starting from 6 months prior to LMP, OR Documentation that the patient was exposed to glatiramer acetate (e.g., Copaxone) at any point starting from 6 months prior to LMP (through the first trimester)	
	Patient agrees to sign the Release of Medical Information Form permitting the study to contact her HCP(s) and the pediatric HCP for medical information	
	Is the outcome of the pregnancy (i.e., pregnancy loss or live birth) known?	
Demographics and Characteristics	Maternal age (years)	
	Paternal age (years)	
	Race/ethnicity	
	Education level	Specify categories
	Height	Units of cm or inches and feet
	Weight	Units of lbs. or kg
	BMI	Calculated using height and weight
Lifestyle Risk Factors	Cigarette and tobacco use	Current, former, never; if current or former, regular or occasional use?
	Caffeine consumption	Y/N; if yes, how many caffeinated beverages (e.g., coffee) per day over the last week?
	Alcohol consumption	Drinks/week
	Illicit drug use	Y/N, then choose type of illicit drug
Current Pregnancy	Date of LMP	Calendar provided to help recall
	EDD	Calendar provided to help recall

Variable Category	Data Elements	Additional Information
	Date and results of any prenatal testing	Calendar provided to help recall rubella titer, toxoplasmosis, venereal disease, hepatitis, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein, glucose
Medical History		
Pregnancy History	Parity	
	Gravidity	
	Previous preterm births	
	Previous spontaneous abortions	
	Previous elective or therapeutic terminations (and reason, if any given)	
	History of any congenital malformations	
	Other (please specify)	Free text field (e.g., neonatal sepsis, birth trauma and birth asphyxia)
Surgical History	Past surgical procedures and date(s)	Any
Medical Conditions (other than MS)	(e.g. Diabetes, high blood pressure, malignancy)	
	Diagnosis	
	Start date(s)	
	End date(s)	
	Disease duration (calculated field)	
MS Disease	Date of first MS symptom	
	Diagnosis date	
	Date of most recent relapse	Or patient did not have any relapses. If yes, Total number of relapses experienced within the past 12 months, 2 years, and 3 years
	MS subtype	
	Disease duration (calculated field)	

Variable Category	Data Elements	Additional Information
	EDSS score (if available)	
Prior MS Treatment	Drug name	Multiple entries allowed
	Start date(s)	
	End date(s)	
	Dose	
	Reason for stopping treatment	
Family Reproductive History	Baby's father/Baby's mother's family/Baby father's family -- ever fathered other pregnancies with any of the following;	Y/N
	Multiple births	
	Congenital malformations	If yes, please specify:
	Spontaneous abortions	
	Premature births	
	Chromosomal anomalies	
	Developmental delays	
Family MS History	Other family members with MS (mother, father, other)	If yes, please specify which family member
	MS type	
	Age at diagnosis	
Ocrelizumab Treatment	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
	Reason for discontinuation (if applicable)	
	Duration of use (calculated field)	
Prior and Current Medications (all medications used from 6 months prior to LMP such as glatiramer	Name of medication	Multiple entries allowed
	Indication	
	Start date(s)	

Variable Category	Data Elements	Additional Information
acetate)	End date(s)	
	Dose	
Vaccinations Received since LMP	Vaccination (name)	
	Vaccination date (with calendar to aid recall)	

BMI = body mass index; EDD = expected date of delivery; EDSS = Expanded Disability Status Scale; HCP = healthcare provider; LMP = last menstrual period; MS = multiple sclerosis

Table 2. Pregnancy Follow-up

Variable Category	Data Elements	Additional Information
Date of Contact		
Reporter of Information	Patient	Contact information (any changes); Secondary contact (if available)
	Obstetrician	Contact information (any changes)
	Neurologist	Contact information (any changes)
	Other (please specify)	Contact information (any changes)
Lifestyle Risk Factors (if changed since last visit)	Cigarette and tobacco use	Current, former, never; if current or former, regular or occasional use?
	Caffeine consumption	Y/N; if yes, how many caffeinated beverages (e.g., coffee) per day over the last week?
	Alcohol consumption	Drinks/week
	Illicit drug use	Y/N, then choose type of illicit drug
Current Pregnancy	Gestational age at contact	
	Date and results of any prenatal testing	Calendar provided to help recall rubella titer, toxoplasmosis, venereal disease, hepatitis, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein, glucose
	Pregnancy outcome and date of outcome, if applicable	Spontaneous abortion Elective or therapeutic termination (reason for elective or therapeutic termination) Live Birth Stillbirth Congenital malformations identified if spontaneous abortion, termination, or stillbirth; Autopsy and/or pathology reports for adverse pregnancy outcomes of stillbirth, spontaneous abortion or termination will be collected and reviewed, if available.
Medical Conditions (other than MS	Condition	e.g., Gestational diabetes, high blood pressure,

Variable Category	Data Elements	Additional Information
since last contact)		malignancy
	Diagnosis	
	Start date(s)	
	End date(s)	
	Disease duration (calculated field)	
MS Disease	Number of relapses since last contact	Date of relapses
	Recent EDSS score (if available)	
Ocrelizumab Treatment	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
	Reason for discontinuation (if applicable)	
	Duration of use (calculated field)	
Other MS Treatment (such as glatiramer acetate, if applicable) Concomitant Medications	Medication name	Multiple entries allowed
	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
Vaccinations Received since Last Contact	Vaccination	
	Vaccination date (with calendar to aid recall)	
Pregnancy-Related SAEs	Event	
	Start date	
	End date	
	Ongoing	
	Seriousness	

Variable Category	Data Elements	Additional Information
	Severity	
	Relationship to ocrelizumab	
	Relationship to glatiramer acetate	
	Outcome	
	Action taken	

EDSS = Expanded Disability Status Scale; HCP = healthcare provider; MS = multiple sclerosis; SAE = serious adverse event

Table 3. Birth Information (approximately 4 weeks after EDD)

Variable Category	Data Elements	Additional Information
Date of Contact	Date	
Reporter of Information	Patient	Contact information (any changes); Secondary contact (if available)
	Obstetrician	Contact information (any changes)
	Neurologist	Contact information (any changes)
	Infant HCP	Contact information
	Other (please specify)	Contact information (any changes)
Date of Pregnancy Outcome	Date	
	Gestational age (calculated field)	
Pregnancy Outcome	Spontaneous abortion Elective or therapeutic termination (reason for elective or therapeutic termination) Live birth Stillbirth Congenital malformations identified if spontaneous abortion, termination, or stillbirth	Reason for elective or therapeutic termination, if known; Autopsy and/or pathology reports for adverse pregnancy outcomes of stillbirth, spontaneous abortion or termination will be collected and reviewed, if available.
Mode of Delivery	Vaginal delivery Assisted delivery Cesarean section	Anesthesia used, if applicable
Lifestyle Risk Factors (if changed since last visit)	Cigarette and tobacco use	Current, former, never; if current or former, regular or occasional use?
	Caffeine consumption	Y/N; if yes, how many caffeinated beverages (e.g., coffee) per day over the last week?
	Alcohol consumption	Drinks/week
	Illicit drug use	Y/N, then choose type of illicit drug
Medical Conditions (other than MS since last contact)	Condition	e.g., Gestational diabetes, high blood pressure, malignancy

Variable Category	Data Elements	Additional Information
	Diagnosis	
	Start date(s)	
	End date(s)	
	Disease duration (calculated field)	
MS Disease	Number of relapses since last contact	Date of relapses
	Recent EDSS score (if available)	
Ocrelizumab Treatment	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
	Reason for discontinuation (if applicable)	
	Duration of use (calculated field)	
Other MS Treatment (such as glatiramer acetate, if applicable) Concomitant Medications	Medication name	Multiple entries allowed
	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
Patient Vaccinations Received since Last Contact	Vaccination and date (with calendar to aid recall)	
Infant Vaccinations Received since Last Contact	Vaccination and date (with calendar to aid recall)	
Pregnancy-Related SAEs	Event	
	Start date	
	End date	
	Ongoing	
	Seriousness	

Variable Category	Data Elements	Additional Information
	Severity	
	Relationship to ocrelizumab	
	Relationship to glatiramer acetate	
	Outcome	
	Action taken (limited to hospitalization)	
Infant SAEs and severe infections of NCI CTCAE Grade 3	Event	
	Start date	
	End date	
	Ongoing	
	Seriousness	
	Severity	
	Relationship to ocrelizumab	
	Relationship to glatiramer acetate	
	Outcome	
	Action taken	
Infant Characteristics	Date of birth, gestational age at birth (calculated field)	
	Sex	
	Weight	
	Length	
	Head circumference	
	Birth order (for multiple births), and number of fetuses	
	Laboratory values, if available (e.g., CD19, neutrophil, lymphocyte, white blood cell, immunoglobulin, and platelet counts)	Date, result
	Apgar scores (1, 5, and 10 minutes)	
	Congenital malformations noted (including description and	

Variable Category	Data Elements	Additional Information
	attribution)	
	Infant feeding: breastfed, formula, combination breastfed/formula, other (please describe)	Start and stop dates of exclusive breastfeeding; number of weeks exclusively breastfed since birth (calculated variable)

EDD = expected date of delivery; EDSS = Expanded Disability Status Scale; HCP = healthcare provider; SAE = serious adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

Table 4. Pediatric Follow-up (approximately at infant age 12, 26, and 52 weeks after birth)

Variable Category	Data Elements	Additional Information
Date of Contact	Date	
Reporter of Information	Patient	Contact information (any changes); Secondary contact (if available)
	Obstetrician	Contact information (any changes)
	Neurologist	Contact information (any changes)
	Infant HCP	Contact information (any changes)
	Other (please specify)	Contact information (any changes)
Date of Pregnancy Outcome	Date	
	Gestational age (calculated field)	
Infant Vaccinations Received since Last Contact	Vaccination and date (with calendar to aid recall)	
Infant SAEs and severe infections of NCI CTCAE Grade 3	Event	
	Start date	
	End date	
	Ongoing	
	Seriousness	
	Severity	
	Relationship to ocrelizumab	
	Relationship to glatiramer acetate	
	Outcome	
	Action taken	
Infant Characteristics	Weight	
	Length	
	Head circumference	
	Laboratory values, if available (e.g., CD19, neutrophil, lymphocyte, white blood cell, immunoglobulin, and	Date, result

Variable Category	Data Elements	Additional Information
	platelet counts)	
	Infant feeding: breastfed, formula, combination breastfed/formula, other (please describe)	Number of weeks exclusively breastfed since birth
	Infant development: social/emotional, language/communication, cognitive, movement/physical development milestones	Any identified developmental delays or impairment? If yes, please characterize
	Any new malformation or growth alterations since last visit	Including description and attribution

HCP = healthcare provider; SAE = serious adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

Table 5. Early Termination of Study Participation, if applicable

Variable Category	Data Elements	Additional Information
Date of Contact	Date	
Termination of Study Participation Status	Completion of follow-up Early termination/withdrawal of study participation	Date of withdrawal from study participation, if different from date of contact. Reason for withdrawal from study participation, if provided (lost to follow-up, adverse event [please specify], or other [please specify])
Reporter of Early Termination of Study Participation	Patient	Contact information (any changes); Secondary contact (if available)
	Obstetrician	Contact information (any changes)
	Neurologist	Contact information (any changes)
	Infant HCP	Contact information (any changes)
	Other (please specify)	Contact information (any changes)
Date of Pregnancy Outcome	Date	
	Gestational age (calculated field)	
Ocrelizumab Treatment	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
	Reason for discontinuation (if applicable)	
	Duration of use (calculated field)	
Other MS Treatment (such as glatiramer acetate, if applicable) Concomitant Medications	Medication name	Multiple entries allowed
	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	

Variable Category	Data Elements	Additional Information
Pregnancy Outcome	Spontaneous abortion Elective or therapeutic termination (reason for elective or therapeutic termination) Live Birth Stillbirth Congenital malformations identified if spontaneous abortion, termination, or stillbirth	Reason for elective or therapeutic termination, if known; Autopsy and/or pathology reports for adverse pregnancy outcomes of stillbirth, spontaneous abortion or termination will be collected and reviewed, if available.
Pregnancy-Related SAEs	Event	
	Start date	
	End date	
	Ongoing	
	Seriousness	
	Severity	
	Relationship to ocrelizumab	
	Relationship to glatiramer acetate	
	Outcome	
	Action taken (limited to hospitalization)	
Infant SAEs and severe infections of NCI CTCAE Grade 3	Event	
	Start date	
	End date	
	Ongoing	
	Seriousness	
	Severity	
	Relationship to ocrelizumab	
	Relationship to glatiramer acetate	
	Outcome	
	Action taken	

Variable Category	Data Elements	Additional Information
Infant Characteristics	Date of birth, gestational age at birth (calculated field)	
	Sex	
	Weight	
	Length	
	Head circumference	
	Laboratory values, if available (e.g., CD19, neutrophil, lymphocyte, white blood cell, immunoglobulin, and platelet counts)	Date, result
	Birth defects noted (including description and attribution)	
	Infant feeding: breastfed, formula, combination breastfed/formula, other (please describe)	Number of weeks exclusively breastfed since birth
	Infant development: social/emotional, language/communication, cognitive, movement/physical development milestones	Any identified developmental delays or impairment? If yes, please characterize
	Any new malformation or growth alterations since last visit	
	Hospitalizations since last visit	Date, primary diagnosis at discharge (please specify)

HCP = healthcare provider; SAE = serious adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

Appendix 4
Methods for Assessing and Recording Adverse Events

4.1 Assessment of Severity of Adverse Events

4.2 Assessment of Causality of Adverse Events

4.3 Procedures for Recording Adverse Events

Appendix 4.1 Assessment of Severity of Adverse Events

The adverse event (AE) severity grading scale for the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (v4.0) will be used for assessing AE severity. The table below will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to AE [d]

AE = adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

Note: Based on the NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (SAE) (see Section 11.1.3.1 for reporting instructions), per the definition of SAE in Section 11.1.1.1.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 11.1.3.1 for reporting instructions), per the definition of SAE in Section 11.1.1.1.

Appendix 4.2 Assessment of Causality of Serious Adverse Events

Physicians should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not a serious adverse event (SAE) is considered to be related to the study medicines, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study medicines
- Course of the event, especially considering the effects of dose reduction, discontinuation of study medicines, or reintroduction of study medicines (when applicable)
- Known association of the event with the study medicines or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each of the medicinal products.

Appendix 4.3 Procedures for Recording Serious Adverse Events

Appendix 4.3.1 Diagnosis versus Signs and Symptoms

For pregnancy-related SAEs, a diagnosis (if known) should be recorded in the pregnancy-related SAE section of the electronic Case Report Form (eCRF) rather than individual signs and symptoms (e.g., ectopic pregnancy or spontaneous abortion rather than pelvic pain, vaginal bleeding, or fainting). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the pregnancy-related SAE section of the eCRF. If a diagnosis is subsequently established, all previously reported pregnancy-related SAEs based on signs and symptoms should be nullified and replaced by one pregnancy-related SAE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Appendix 4.3.2 Adverse Events Occurring Secondary to Other Events

In general, pregnancy-related SAEs that are secondary to other events (e.g., retroplacental hemorrhage or death in utero) should be identified by their primary cause, with the exception of serious secondary events. A medically significant secondary

pregnancy-related SAE that is separated in time from the initiating event should be recorded as an independent event in the SAE section of the eCRF. For example:

- If preeclampsia results in swelling in the feet, legs, or hands, only preeclampsia should be reported on the eCRF.
- If preeclampsia leads to preterm birth, both events should be reported separately on the eCRF.
- If an infant birth defect is accompanied by a small size for gestational age, both events should be reported separately on the eCRF.

All SAEs related to pregnancy and/or pregnancy outcomes should be recorded separately in the SAE section of the eCRF if it is unclear as to whether the events are associated.

Appendix 4.3.3 Abnormal Laboratory Values

A laboratory test result must be reported only if it fulfils the criteria of a pregnancy-related SAE as outlined in the protocol (e.g., is accompanied by clinical symptoms or results in a medical intervention [e.g., potassium supplementation for hypokalemia]). In this circumstance, it should be recorded on the SAE section of the eCRF. Furthermore, if the laboratory test (serious or non-serious, and whether or not accompanied by any clinical symptom) may be suggestive of immune suppression in the neonate or infant, (e.g., neutropenia, lymphopenia, leukopenia, thrombocytopenia, hypogammaglobulinemia, decreased B-lymphocyte CD19 count, low vaccine-induced response titer), it needs to be recorded on the eCRF.

It is the physician's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as a pregnancy-related SAE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., blood Rh factor incompatibility associated with Rhesus disease), only the diagnosis (i.e., Rhesus disease) should be recorded on the SAE section of the eCRF. If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the SAE section of the eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "low platelet count," as opposed to "abnormal platelet count"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the pregnancy-related SAE. For example, a low platelet count of 100 x 109/L of blood should be recorded as "thrombocytopenia".

Appendix 4.3.4 Abnormal Vital Sign Values

A vital sign result must be reported as a pregnancy-related SAE if it meets the criteria as outlined in the protocol.

It is the physician's responsibility to review all vital sign findings.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., low blood pressure and loss of consciousness), only the diagnosis (i.e., hypotension) should be reported following standard pharmacovigilance practices.

Appendix 4.3.5 Deaths

All deaths that occur during the protocol-specified SAE reporting period (see Section 11.1.2.1), regardless of relationship to study medicines, must be recorded in the SAE section of the eCRF and immediately reported to Roche (see Section 11.1.3.1).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE section of the eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the SAE section of the eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Appendix 4.3.6 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions section in the eCRF.

A preexisting medical condition should only be reported as an SAE related to pregnancy if the frequency, severity, or character of the condition worsens during the study. When reporting such events on the SAE section of the eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Appendix 4.3.7 Hospitalization or Prolonged Hospitalization

Any pregnancy-related SAE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 11.1.1.1), except as outlined below.

All other hospitalizations should be reported as appropriate following standard pharmacovigilance practices.