PASS Information

Title	Ublituximab Pregnancy Registry: A Prospective Study of Pregnancy and Infant Outcomes in Patients Treated with ublituximab
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Joint PASS	No
Research question and objectives	The primary objective of the ublituximab Pregnancy Registry is to compare the maternal, fetal, and infant outcomes of pregnant individuals with multiple sclerosis (MS) who are exposed to ublituximab during pregnancy with outcomes of an internal comparison cohort of pregnant individuals with MS who are not exposed to ublituximab or other anti-CD20 monoclonal antibodies at any time during pregnancy.
Country(-ies) of study	United States
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Marketing authorisation holder(s)

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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
ACOG	American College of Obstetricians and Gynecologists
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ART	Assisted reproductive technology
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CIS	Clinically isolated syndrome
CNS	Central nervous system
DMT	Disease-modifying therapy
DOC	Date of conception
EDD	Estimated date of delivery
Fc	Fragment crystallizable
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
HCP	Healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
IFN	Interferon
Ig	Immunoglobulin
IPW	Inverse probability weighting
IRB	Institutional review board
LMP	Last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major congenital malformation
MS	Multiple sclerosis
NK	Natural killer
NVSS	National Vital Statistics System
PI	Prescribing information
RR	Relative risk

Abbreviation or Term	Definition
RRMS	Relapsing-remitting multiple sclerosis
SAB	Spontaneous abortion
SAC	Scientific advisory committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SGA	Small for gestational age
SOP	Standard operating procedure
SPMS	Secondary progressive multiple sclerosis
TERIS	Teratogen Information System
US	United States
VRCC	Virtual research coordination center[a]

Note: Abbreviations used only in tables, figures, or an appendix are defined in the table or figure footnotes or the appendix.

3. RESPONSIBLE PARTIES

Name, Degree(s)	Title/Role	Affiliation
Syd Phillips, MPH,	Principal Investigator	PPD, part of Thermo Fisher Scientific
Edward Fox, MD, PhD	Medical Oversight	TG Therapeutics, Inc.
Jackie Parker, MPH	Vice President, Clinical Operations and Pharmacovigilance	TG Therapeutics, Inc.

4. ABSTRACT

Name of Sponsor:	TG Therapeutics, Inc.
Name of product:	BRIUMVI™ (ublituximab)
Title of Study:	BRIUMVI™ Pregnancy Registry: A Prospective Study of Pregnancy and Infant Outcomes in Patients Treated with BRIUMVI™
Study Number:	TG1101-RMS403
Study Phase:	Post-marketing Observational Pregnancy Registry
Location:	United States
Primary Objective:	The primary objective of the BRIUMVI™ Pregnancy Registry is to compare the maternal, fetal, and infant outcomes of pregnant individuals with multiple sclerosis (MS) who are exposed to BRIUMVI™ during pregnancy with outcomes of an internal comparison cohort of pregnant individuals with MS who are not exposed to BRIUMVI™ or other anti-CD20 monoclonal antibodies at any time during pregnancy.

Methodology:

The BRIUMVI™ Pregnancy Registry is a prospective, observational cohort study designed to evaluate the association between BRIUMVI™ exposure during pregnancy and subsequent maternal, fetal, and infant outcomes. The outcomes of interest include major congenital malformations (MCMs; primary outcome), minor congenital malformations, gestational hypertension, pre-eclampsia, eclampsia, gestational diabetes, spontaneous abortions (SAB), stillbirths, elective terminations, small for gestational age (SGA), preterm births, postnatal growth deficiency, infant developmental delays, infant serious or opportunistic infections, and infant hospitalizations.

Pregnancy outcomes will be assessed throughout pregnancy, with data collection occurring at enrollment, the end of the second trimester, and pregnancy outcome. Infant outcomes will be assessed throughout the infant's first year of life, with active data collection by the registry occurring at 4 and 12 months after delivery. Enrolled pregnant individuals and the healthcare providers (HCPs) involved in their care or the care of their infants, if applicable, will serve as data reporters to the registry. The study is strictly observational; the schedule of office visits and all treatment regimens will be determined by HCPs. Only data that are documented in patients' medical records during the course of medical care will be collected. No additional laboratory tests or HCP assessments will be required as part of this registry.

Number of Participants (planned):

The registry aims to enroll a total of 728 pregnant individuals, with 364 individuals in each cohort. This sample size will afford the study the ability to detect a 3-fold increase in the prevalence of the primary outcome, MCM, in the exposed cohort with 80% power.

Study Population:

The study population will include 2 internal cohorts of pregnant individuals with MS and 1 "external cohort" representing the general population in the US. The internal study population will include pregnant individuals 15–50 years of age who provide consent to participate in the study, agree to medical releases for their HCPs to provide data to the registry, and meet the criteria for inclusion into 1 of the following cohorts:

- Exposed cohort: Pregnant individuals with MS who are exposed to BRIUMVI™ at any time during pregnancy
- Unexposed cohort: Pregnant individuals with MS who are not exposed to BRIUMVI™ or other anti-CD20 monoclonal antibodies at any time during pregnancy but who may be exposed to other products for the treatment of MS

Individuals will be eligible for enrollment but excluded from the analysis population if the pregnancy outcome occurred prior to first contact with the registry, or if they have been exposed to teratogens and/or investigational medications during pregnancy. However, these individuals will be included in supplementary analyses.

In addition, the registry will use background rates from population-based surveillance systems or the published literature as external comparators.

Duration of Participation:

For each enrolled pregnant individual, participation will begin at enrollment and end at pregnancy outcome (if fetal loss) or 12 months after pregnancy outcome (if live birth).

Statistical Methods:

Analyses will be conducted in accordance with the study objectives, statistical analysis plan (SAP), table/listing shells, and applicable guidelines. Registry data will be summarized in tables and listings by study cohort, as appropriate. Comparisons of demographic and baseline characteristics and prevalence rates of the outcomes of interest will be conducted between the study cohorts.

Demographic and baseline characteristics will be summarized with descriptive statistics, and balance between cohorts will be assessed using standardized differences. These data will be presented before and after the data are balanced with the inverse probability weighting (IPW) method. In addition, within each cohort, the demographic and baseline characteristics of those included in the analysis population will be compared with those excluded from the analysis population for being lost to follow-up, retrospectively enrolled, or exposed to teratogens or investigational medications during pregnancy.

Formal quantitative comparisons of prevalence rates of the outcomes of interest will be conducted between the exposed and unexposed cohorts. For each outcome, if the number of events permits, results will be presented for unadjusted and adjusted models. Relative risks (RRs) will be reported along with their 95% confidence intervals. Adjusted methods will incorporate weights estimated using the IPW method to balance the cohorts with regard to observable pre-exposure covariates. The adjusted comparison of prevalence rates of MCMs observed in the exposed and unexposed cohorts will be considered the primary analysis.

Subgroup analyses may be conducted that consider the timing and extent of exposure, and maternal age group at conception. Supplementary analyses will be conducted that include pregnant individuals who were excluded from the analysis population due to the occurrence of the pregnancy outcome prior to enrollment (retrospectively enrolled participants) or exposure to a teratogen or an investigational medication during or prior to pregnancy (teratogen/investigational medication-exposed participants).

The prevalence of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome, based on clinical knowledge. For most outcomes, the analysis population (denominator) will be the number of pregnancies with pregnancy outcome data, the number of live births, or the number of infants with follow-up data at the timepoint of interest, as appropriate; however, for some outcomes, the analysis population (denominator) will be restricted on the basis of certain relevant factors.

Sensitivity analyses will also be conducted to examine the extent to which changes in certain methods or assumptions affect the results. For example, a sensitivity analysis will be conducted that applies a stricter definition of prospective enrollment, which is based on the timing of prenatal testing relative to enrollment.

Analyses will also be conducted to compare the prevalence rates of the outcomes of interest in the exposed cohort with those of selected external comparators (e.g., Centers for Disease Control and Prevention's Metropolitan Atlanta Congenital Defects Program [Metropolitan Atlanta Congenital Defects Program] and National Vital Statistics System [NVSS]).

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Date of study registration in the HMA-EMA Catalogues	Anticipated within one month after protocol approval
Start of data collection	May 2024
Annual/Period progress report submission in PBRER*	March 2025 March 2026 March 2027 March 2028 March 2029 March 2030 March 2031 March 2032 March 2033 March 2034
Interim study report submission (cumulative up to data cut-off)*	March 2030 March 2032
End of data collection	March 2035
Final study report submission*	March 2036

*Data cut-off: 27 Dec of the report year
PBRER: Periodic Benefit Risk Evaluation Report

7. RATIONALE AND BACKGROUND

7.1. BRIUMVI™

BRIUMVI™ is a recombinant chimeric monoclonal immunoglobulin (Ig) G1 antibody with reduced fucose content directed against CD20-expressing B-cells (BRIUMVI™ Prescribing information [PI]). BRIUMVI™ has a unique protein sequence and targets epitopes on CD20 that are not targeted by other anti-CD20 antibodies used in multiple sclerosis (MS) (i.e., ocrelizumab, ofatumumab, rituximab).

BRIUMVI™ is glycoengineered, producing a low fucose content in its fragment crystallizable (Fc) region. The exclusion of specific fucose molecules in the Fc region enhances its affinity for all variants of FcγRIIIa receptors, activates natural killer (NK)-cell function, and results in enhanced antibody-dependent cellular cytotoxicity (ADCC) relative to other approved CD20 antibodies. In in vitro studies, BRIUMVI™ demonstrated 25 to 30 times increased ADCC relative to other anti-CD20 therapies.

7.2. Multiple Sclerosis

7.2.1. Description and Epidemiology

MS is an idiopathic, chronic, inflammatory demyelinating disease of the central nervous system (CNS) with genetic and environmental risk factors. The disease is characterized pathologically by inflammatory lesions of CNS myelin with resultant edema, demyelination, and oligodendrocyte and neuronal loss. Acute inflammatory lesions are initiated by activated peripheral lymphocytes that enter the CNS through a breached blood-brain barrier.

The prevalence of MS is increasing, and an estimated 1 million people in the United States (US) and 2.8 million worldwide have the disease (Multiple Sclerosis International Federation 2020). Approximately three-quarters of patients with MS are women, and it is estimated that between one-fifth and one-third of women with MS deliver a child after disease onset (Houtchens 2018). The clinical signs and symptoms of MS can occur in isolation or in combination, and can include weakness, spasticity, gait and coordination imbalances, sensory dysfunction, vision loss, sexual dysfunction, fatigue, depression, chronic pain, sleep disorders, and cognitive impairment (Tanasecu 2014).

There are 4 types/disease courses for MS (clinically isolated syndrome [CIS], relapsing-remitting multiple sclerosis [RRMS], secondary progressive multiple sclerosis [SPMS], and primary progressive MS), but most people (85%) are initially diagnosed with RRMS (European Medicines Agency 2015).

7.2.2. Current Standard of Care

Control of relapses and reduction of inflammatory burden the primary focus of therapy, as there is currently no cure for MS. Therapies include symptomatic treatments (e.g., steroids, muscle relaxants, antidepressants, anti-infectives) and those that alter the course of the disease (disease-modifying therapies [DMTs]). The goal of treating relapsing forms of MS with DMTs is to reduce the rate of relapses and disease activity and to delay disability progression. Optimization of outcomes using early intervention with highly effective DMTs is increasingly recognized as

an important treatment strategy to reduce long-term physical and cognitive disability, thereby improving the patient's overall quality of life (Giovannoni 2016).

There are several DMTs available for the treatment of MS with different mechanisms of action and differentiated efficacy and safety profiles. These include (1) the first-approved DMTs (interferon [IFN]–β-1a, IFN-β-1b, and glatiramer acetate), (2) oral therapies (S1P modulators including fingolimod, siponimod, ponesimod, and ozanimod; monomethyl fumarate; diroximel fumarate; dimethyl fumarate; teriflunomide; and cladribine), and (3) monoclonal antibodies (alemtuzumab, ocrelizumab, ofatumumab, and natalizumab) (Varytė 2021). Each treatment is tailored to patient preferences, monitoring recommendations, drug- and individual-specific risk factors, and concerns regarding the long-term risk of MS related disability and morbidity.

7.2.3. Multiple Sclerosis Treatments and Adverse Pregnancy Outcomes

An analysis of post-marketing safety surveillance data from patients exposed to IFN-β-1a or IFN-β-1b during pregnancy revealed that rates of spontaneous abortions (SABs) and major congenital malformations (MCMs) among prospectively reported pregnancies were consistent with those of the general population (Sandberg-Wollheim 2011; Coyle 2014). Though it is generally advised that DMTs be stopped prior to conception, the IFNs and glatiramer acetate are thought to be incapable of crossing the placenta and have been on the market for years without any significant issues reported for pregnancy exposures. They are therefore considered to be safe for use during pregnancy if necessary for disease management (Coyle 2016).

Pregnancy outcomes in women with MS exposed to fingolimod shortly before or during pregnancy were prospectively collected in cases from clinical trials, observational studies, surveillance programs, and spontaneous reports. Although congenital cardiac and renal anomalies were observed, the prevalence of major malformations among live births did not appear to be significantly higher than in the general population and the unexposed MS population. Proportions of miscarriage were in line with those of the general and unexposed MS populations, and no specific pattern of birth defects was identified (Geissbühler 2018).

Data from populations of women with MS exposed to other MS-specific medications are limited (Geissbühler 2018). The prevalence of major congenital malformations (MCMs) observed in pregnant females exposed to natalizumab, glatiramer acetate, and IFN-β were similar to corresponding observations with fingolimod, with overlapping confidence intervals (CIs). No birth defects were observed in cases exposed to teriflunomide or dimethyl fumarate in a limited number of pregnancies (Kieseier 2014; Hellwig 2021).

Monoclonal antibodies are some of the newest therapies to gain approval for the treatment of MS. In 2016, the Tysabri Pregnancy Exposure Registry reported a major birth defect rate among women exposed to natalizumab during pregnancy that was slightly higher than the Metropolitan Atlanta Congenital Defects Program (MACDP) external reference rate; however, no specific pattern of malformations suggested a drug effect. The rate of SABs reported in the registry was consistent with that of the general population (Friend 2016). Some of the newest medications, including anti-CD20 and anti-CD25 monoclonal antibodies, are predicted to actively transport across the placenta during the second trimester and have raised some concerns about potential immune implications for the developing fetus. In studies of rituximab, animal models showed

transient B-cell depletion, and the same phenomenon has been periodically observed in human case studies. However, the available evidence suggests this may resolve within the first 6 months of life with no lasting consequences (Coyle 2016; Dobson 2023).

7.2.4. Multiple Sclerosis and Adverse Pregnancy, Delivery, and Neonatal Outcomes

There are few studies examining the association between MS and adverse pregnancy outcomes, and when available, the results have been inconsistent. In one retrospective study of administrative data in California, the authors reported an increased risk of urinary tract infections, induction of labor, and cesarean delivery among patients with MS, but no increased risk for other outcomes (Fong 2018). However, similar studies in the US have reported elevated risks of infection during pregnancy (2 studies), premature labor (1 study), preterm delivery (1 study), cesarean delivery (2 studies), intrauterine growth restriction (1 study), and congenital malformations (1 study) among women diagnosed with MS (Houtchens 2018; Kelly 2009; MacDonald 2018). Likewise, a retrospective, registry-based study in Norway found that patients with MS gave birth to neonates with reduced birth weight for gestational age, and these patients also had a higher risk of induction of labor and operative intervention during delivery (Dahl 2005). It should be noted that these studies did not take into account MS treatment patterns, so the increased risks may be attributable to the disease and/or the medications used to treat it.

7.3. Potential Risks Associated with Pregnancy Exposure to BRIUMVI™

7.3.1. Animal Data

Weekly intravenous administration of BRIUMVI™ to pregnant monkeys during the first, second, or third trimester of pregnancy resulted in embryofetal loss; administration during the second trimester resulted in external, skeletal, and visceral abnormalities in infants (BRIUMVI™ PI 2022).

Weekly intravenous administration of ublituximab (0 or 30 mg/kg) to separate groups of pregnant monkeys during the first, second, or third trimester of pregnancy produced a severe immunogenic response in dams, resulting in maternal morbidity, death, and embryofetal loss. Dosing was terminated in dams after only 2 doses during the third trimester because of multiple deaths during the first and second trimesters.

Ublituximab-related external, viscera, and skeletal abnormalities occurred in 2 infants from dams exposed during the second trimester of pregnancy. Histopathology evaluations revealed minimal to moderate degeneration/necrosis in the brain. Findings in infants included contractures and abnormal flexion of multiple limbs and tail, shortened mandible, elongated calvarium, enlargement of ears, and/or craniomandibular abnormalities, which were attributed to brain necrosis. Abnormalities were absent in infants of dams exposed during the first trimester of pregnancy. A no-effect dose for adverse effects on embryofetal development in monkeys was not identified (BRIUMVI™ PI 2022).

7.3.2. Clinical Trial Data

There are no data on the developmental risk associated with the use of BRIUMVI™ in pregnant women. Data from case reports of pregnancies occurring during clinical trials with BRIUMVI™

are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Although there are no data on BRIUMVI™, monoclonal antibodies can be actively transported across the placenta, and BRIUMVI™ may cause immunosuppression in the in-utero-exposed infant (BRIUMVI™ PI 2022).

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses and peaks during the third trimester. There are no data on B-cell levels in human neonates following maternal exposure to BRIUMVI™. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy (BRIUMVI™ PI 2022).

7.4. Study Rationale

Currently, there are no adequate and well-controlled clinical studies of BRIUMVI™ in pregnant individuals, and available human data on BRIUMVI™ exposure during pregnancy are insufficient to inform risk analysis. The goal of the registry is to provide information on maternal, fetal, and infant outcomes following exposure to BRIUMVI™ during pregnancy, so that patients and physicians can weigh the benefits and risks of exposure to BRIUMVI™ during pregnancy and make informed treatment decisions.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Study Objectives

The objective of the BRIUMVI™ Pregnancy Registry is to compare the maternal, fetal, and infant outcomes of pregnant individuals with MS who are exposed to BRIUMVI™ during pregnancy with the outcomes of an internal comparison cohort of pregnant individuals with MS who are unexposed to BRIUMVI™ or other anti-CD20 monoclonal antibodies during pregnancy but who may be exposed to other products for the treatment of MS.

- The primary objective of the registry is to compare the prevalence rate of MCMs between the 2 cohorts.
- Secondary objectives of the registry are:
  - To compare the prevalence rates of the secondary outcomes (Section 8.2) between the cohorts.
  - To compare the prevalence rates of the primary and secondary outcomes in the exposed cohort to rates in the general population from the published literature.

8.2. Study Outcomes

The primary and secondary outcomes are listed below. Section 9.3.3 provides the definitions and ascertainment methods of these outcomes.

Primary outcome:

- MCM

Secondary outcomes:

Pregnancy outcomes

- Minor congenital malformations
- Gestational hypertension
- Pre-eclampsia
- Eclampsia
- Gestational diabetes
- SAB
- Stillbirth
- Elective termination
- Preterm birth

Foetal/infant outcomes

- Small for gestational age (SGA)
- Postnatal growth deficiency

- Infant developmental delay
- Infant serious or opportunistic infections
- Infant hospitalizations

9. RESEARCH METHODS

9.1. Study design

9.2. The BRIUMVI™ Pregnancy Registry is a US-based, prospective, observational cohort study designed to evaluate the association between BRIUMVI™ exposure during pregnancy and subsequent maternal, fetal, and infant outcomes. Based on study enrollment and approval of BRIUMVI™ in ex-US countries, the registry may be expanded to countries outside the US. Participation in the registry is voluntary, and participants can withdraw their consent to participate at any time. Data will be collected from enrolled pregnant individuals and the healthcare providers (HCPs) involved in their care or the care of their infants, if applicable. The registry is strictly observational; the schedule of office visits and all treatment regimens will be determined by HCPs. Only data that are documented in patients' medical records during the course of medical care will be collected. No additional laboratory tests or HCP assessments will be required as part of this registry. The design of this pregnancy registry is consistent with relevant guidelines and recommendations (FDA 2019; European Medicines Agency 2005).Setting

9.2.1. Study Duration and Follow-up

The registry will be launched following submission to the FDA and institutional review board (IRB) approval of the protocol. Enrollment of individuals in the registry and data collection are expected to occur over approximately 10 years; however, the duration of the study may be extended if enrollment targets are not met by the planned completion date.

For each enrolled pregnant individual, participation will begin at enrollment and end at pregnancy outcome (if fetal loss: SAB, stillbirth, or elective termination) or 12 months after pregnancy outcome (if live birth).

9.2.2. Study Population

The study population will include 2 internal cohorts of pregnant individuals with MS and 1 "external cohort" of unexposed women without MS representing the general population in the US.

9.2.2.1. Internal Study Population Enrollment Criteria

The internal study population will include pregnant individuals 15–50 years of age who provide consent to participate, who provide medical releases for their HCPs to provide data to the registry, and who meet the criteria for inclusion into one of the registry cohorts.

Individuals will be eligible for enrollment but excluded from the analysis population if the pregnancy outcome occurred prior to first contact with the registry or if they have been exposed to teratogens and/or investigational medications during pregnancy. However, these individuals will be included in supplementary analyses.

The internal study population will include 2 cohorts of pregnant individuals with MS: one cohort that is exposed to BRIUMVI™ and 1 cohort that is unexposed to BRIUMVI™ but that may be exposed to other products for the treatment of MS. Table 1 summarizes the inclusion and exclusion criteria for each cohort.

Table 1: Internal Study Population

Cohort	Inclusion Criteria[a]	Exclusion Criteria for Enrollment	Exclusion Criteria for Enrollment
Exposed cohort: Pregnant individuals diagnosed with MS who are exposed to BRIUMVI™ at any time during pregnancy[b]	• Individual 15-50 years of age • Currently or recently (within 1 year of pregnancy outcome) pregnant • Diagnosis of MS • Consent to participate • Authorization for her HCP(s) to provide data to the registry • Exposure to at least 1 dose of BRIUMVI™ at any time during pregnancy[b]	• Prior to enrollment, exposure to other anti-CD20 monoclonal antibodies at any time during pregnancy[c]	• Occurrence of pregnancy outcome prior to first contact with the VRCC (retrospectively enrolled) • After enrollment, exposure to anti-CD20 monoclonal antibodies other than BRIUMVI™ at any time during pregnancy[c] • Exposure to teratogens and/or investigational medications during pregnancy • Lost to follow-up
Unexposed cohort: Pregnant individuals diagnosed with MS who are not exposed to BRIUMVI™ or other anti-CD20 monoclonal antibodies at any time during pregnancy but who may be exposed to other products for the treatment of MS	• Individual 15–50 years of age • Currently or recently (within 1 year of pregnancy outcome) pregnant • Diagnosis of MS • Consent to participate	• Prior to enrollment, exposure to anti-CD20 monoclonal antibodies at any time during pregnancy[c]	• Occurrence of pregnancy outcome prior to first contact with the VRCC (retrospectively enrolled) • After enrollment, exposure to anti-CD20 monoclonal antibodies at any

Cohort	Inclusion Criteria[a]	Exclusion Criteria for Enrollment	Exclusion Criteria for Enrollment
	• Authorization for her HCP(s) to provide data to the registry • No exposure to BRIUMVI™ at any time during pregnancy[b]		time during pregnancy[c] • Exposure to known teratogens and/or investigational medications during pregnancy • Lost to follow-up

Abbreviations: HCP = healthcare provider; MS = multiple sclerosis; VRCC = virtual research coordination center
[a] Text italicized to highlight differences between cohorts.
[b] Exposure is defined as bodily uptake of any dose of BRIUMVI™ at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within 6 months of the date of conception).
[c] Exposure is defined as bodily uptake of any dose of anti-CD20 monoclonal antibody at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within 5 half-lives of the date of conception).

9.2.2.2. External Study Population

For external comparators, the registry will use background rates from population-based surveillance systems or the published literature, as described below. It is important to note that such studies may vary in methodology, ascertainment, and classification of birth defects or other pregnancy outcomes, as well as in geographic location, sample size, and other factors that could affect the results of any formal comparisons. Therefore, quantitative comparisons between the registry and external data may be difficult to interpret. Although there are inherent challenges with comparing registry data with data from external sources, these comparisons are not unrealistic and are generally considered acceptable as long as the methodologies of the external comparators are taken into consideration during the analysis (Honein 1999; Kennedy 2004; FDA 2019).

Table 2 shows the study outcomes for which reliable external comparators have been identified. Other appropriate external comparators may be identified during the study and along with published literature to obtain background data for the maternal, fetal, and infant outcomes evaluated in this study. The most up-to-date data available will be used for each study report.

Table 2: External Comparators

Outcome	External Comparator	Current Rate	Reference	Denominator
MCM	CDC MACDP	3.0%	CDC 2008	Live births
Gestational hypertension	US Birth Certificate Data	6.5%	Butwick 2020	Live births
Pre-eclampsia	CDC National Hospital Discharge Survey	3.40%	Ananth 2013	Pregnant individuals

Outcome	External Comparator	Current Rate	Reference	Denominator
Eclampsia	US Birth Certificate Data	0.3%	Butwick 2020	Live births
Gestational diabetes	CDC NVSS	6.9%	Martin 2021	Live births
SAB	Right from the Start	11.8%	Wu 2019	Pregnant individuals
Stillbirth	CDC NVSS	0.6%	Gregory 2021	Live births and stillbirths
Elective termination	Guttmacher Institute	18.4%	Jones 2019	Live births and abortions
Preterm birth	CDC NVSS	8.4%	Osterman 2022	Singleton live births
SGA	N/A	10.0%, by definition	By definition	Singleton live births
Postnatal growth deficiency	N/A	10.0%, by definition	By definition	Singleton infants
Infant developmental delay	Early Childhood Longitudinal Study	13.0%	Rosenberg 2008	Infants

CDC = Centers for Disease Control and Prevention; MACDP = Metropolitan Atlanta Congenital Defects Program; MCM = major congenital malformation; N/A = not applicable; NVSS = National Vital Statistics System; SAB = spontaneous abortion; SGA = small for gestational age.

9.3. Variables

9.3.1. Exposure Definitions and Ascertainment

Exposure to BRIUMVI™ is a condition for inclusion into the exposed cohort. Exposure to BRIUMVI™ during pregnancy is defined as bodily uptake of any dose of BRIUMVI™ at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within 6 months of the date of conception [DOC], based on information in the PI [BRIUMVI™ PI 2022]).

Exposure to comparator products for the treatment of MS during pregnancy is defined as bodily uptake of any dose of comparator product within 5 half-lives prior to conception or during pregnancy.

In addition, exposure to anti-CD20 monoclonal antibodies other than BRIUMVI™ is a condition for exclusion from the study cohorts. Exposure to other anti-CD20 monoclonal antibodies during pregnancy is defined as bodily uptake of any dose of anti-CD20 monoclonal antibodies within 5 half-lives prior to conception or during pregnancy.

Detailed information on dose, route, frequency, dates/duration of exposure, and indication/reason for use will be collected, and exposure will be further categorized by earliest trimester of

exposure. Section 9.3.4 provides information on the methods used to determine gestational age and trimester of exposure.

Exposure information will be updated at each pregnancy follow-up, and changing exposures will be accounted for in the analysis (Section 9.7.2).

9.3.2. Disease Definitions and Ascertainment

A diagnosis of MS is a condition for inclusion into both study cohorts. Disease information, including date of diagnosis, type of MS, and other characteristics (e.g., severity), will be collected from HCPs, based on the HCP's clinical assessment of the patient.

9.3.3. Outcome Definitions and Ascertainment

Table 3 presents the definitions of the outcomes of interest. Additional information on outcome ascertainment is provided for outcomes not simply reported by the HCP.

Table 3: Outcome Definitions and Ascertainment

Outcome	Definition	Ascertainment
Major congenital malformation (MCM)	An abnormality of body structure or function that is present at birth, is of prenatal origin (i.e., birth defect), has significant medical, social, or cosmetic consequences for the affected individual, and typically requires medical intervention (CDC 2020a)	The registry defines and codes MCMs with criteria specified by the CDC MACDP (CDC 2021). a. Exclusion criteria for analyses: To avoid misattribution of the malformation to the medication, MCMs not associated with medication exposure, such as chromosomal abnormalities, genetic syndromes, prematurity-related conditions in infants born at <36 gestational weeks (e.g., patent ductus arteriosus, patent foramen ovale, inguinal hernias, or undescended testes), and positional effects (e.g., hip dislocation due to breech position or abnormal skull shape due to crowding by multiple fetuses), will not be considered MCMs in the statistical analyses (Holmes 2011). b. Adjudication process: A panel of 2 independent experts in clinical genetics and neonatology, blinded to exposure, will review all MCMs reported to the registry and classify them using the CDC's MACDP system. Additionally, the birth defect evaluators will provide their opinions regarding the timing of the development of observed defects. If additional information is needed to aid in classification, the birth defect evaluators will request additional information using the targeted follow-up process outlined in Section 9.6.4. These assessments will be recorded in the database. If there is a discrepancy, a 3rd expert will independently review and code the case, serving as a tiebreaker. These reviews will occur soon after the MCM is reported. Additional reviews will occur if new information is received for the case. Additionally, the SAC will review all MCM cases reported to the registry and reach consensus on the possible temporal association between exposure (to BRIUMVI™) and the development of observed defects. The Sponsor will not be involved in any activities related to case review or adjudication.
Minor congenital malformation	An anomaly or abnormality of body structure that is present at birth, is of prenatal origin (i.e., birth defect), poses no significant health problem in the neonatal period, and tends to have limited social or cosmetic consequences for the affected individual (CDC 2020a)	The registry defines and codes minor congenital malformations with criteria as defined by the CDC (CDC 2019). The same process for adjudicating MCMs will be used to adjudicate minor congenital malformations.

Outcome	Definition	Ascertainment
Spontaneous abortion (SAB)	An involuntary fetal loss or the expulsion of the products of conception occurring at <20 gestational weeks	Section 9.3.4 provides information on the methods used to calculate gestational age.
Stillbirth	As defined by the ACOG, an involuntary fetal loss occurring at ≥20 gestational weeks or, if gestational age is unknown, a fetus weighing ≥350 g (ACOG 2020)	Section 9.3.4 provides information on the methods used to calculate gestational age.
Elective termination	A voluntary fetal loss or interruption of pregnancy that occurs for any reason, including but not limited to, for the preservation of maternal health or due to fetal abnormalities	-
Preterm birth	A live birth occurring at <37 gestational weeks	Section 9.3.4 provides information on the methods used to calculate gestational age.
Small for gestational age (SGA)	Birthweight <10th percentile for sex and gestational age using standard growth charts for full and preterm live born infants (Battaglia 1967)	For the determination of SGA, the registry will utilize the sex-specific international growth reference standards from INTERGROWTH 21st for those born between 240/7 and 426/7 gestational weeks (Villar 2014; Villar 2016). The INTERGROWTH-21st standards are the latest-available global reference standards, representing contemporary information from an international, multiethnic, diverse population, and have been specifically developed for modern research.
Pre-eclampsia	High blood pressure and signs of liver or kidney damage (eg, proteinuria) occurring at >20 gestational weeks (CDC 2020b, ACOG 2002)	-
Eclampsia	Seizures or coma in a pregnant woman with pre-eclampsia (CDC 2020b)	-
Gestational diabetes	Any degree of glucose intolerance with onset or first recognition during pregnancy (ADA 2004)	-
Gestational hypertension	High blood pressure occurring at >20 gestational weeks without signs of liver or kidney damage (eg, proteinuria) (ACOG 2002)	-

Outcome	Definition	Ascertainment
Postnatal growth deficiency	Weight, length, or head circumference in <10th percentile for sex and chronological age using standard growth charts	Postnatal growth deficiency will be evaluated at 4 and 12 months of infant age; deficiencies in weight, length, and head circumference will be evaluated separately. For the determination of postnatal growth deficiency, the registry will utilize the sex-specific international growth reference standards from the WHO for children ages 0 to 59 months. The WHO growth standards are recommended for use in the US for infants and children 0 to 2 years of age (CDC 2010).
Infant developmental delay	Failure to achieve the developmental milestones for chronological age, as defined by the CDC (CDC 2022)	Infant developmental delay will be evaluated at 4 and 12 months of infant age for each CDC-defined category (social/emotional, language/communication, cognitive, and movement/physical development), separately.
Infant serious or opportunistic infections	An infection that occurs within an infant's 1st year of life and is either opportunistic (i.e., occurs more often or is more severe in people with weakened immune systems than in people with healthy immune systems) or serious (i.e., results in significant disability, incapacity, or death; is life-threatening; requires inpatient or prolonged hospitalization; or is considered medically important) (CIOMS 2021; Winthrop 2015)	-
Infant hospitalizations	An inpatient hospital admission occurring in the 1st year of life (CIOMS 2021)	-

Abbreviations: ACOG = American College of Obstetricians and Gynecologists; CDC = Centers for Disease Control and Prevention; CIOMS = Council for International Organizations of Medical Sciences; INTERGROWTH-21st = International Fetal and Newborn Growth Consortium for the 21st Century; MACDP = Metropolitan Atlanta Congenital Defects Program; MCM = major congenital malformation; SAB = spontaneous abortion; SAC = scientific advisory committee; SGA = small for gestational age; US = United States; WHO = World Health Organization

9.3.4. Other Variable Definitions and Ascertainment

Per the American College of Obstetricians and Gynecologists (ACOG), gestational age and the EDD should be determined by the obstetric HCP as soon as data are obtained regarding the LMP, first accurate ultrasound, or both. ACOG considers ultrasound measurement of the embryo or fetus in the first trimester (up to and including $13^{6/7}$ gestational weeks) the most accurate method to establish or confirm gestational age and discourages against changing the EDD based on subsequent ultrasounds. Any pregnancy without an ultrasound before $22^{0/7}$ gestational weeks to confirm or revise the EDD should be considered suboptimally dated. If the pregnancy resulted from ART, the obstetric HCP should use ART-derived gestational age (e.g., based on the age of the embryo and the date of transfer) to determine EDD. ACOG further recommends that the best estimate of EDD by the obstetric HCP, rather than estimates based on LMP alone, be used for research purposes (ACOG 2017).

Based on ACOG's recommendations, the registry will collect the EDD from the obstetric HCP, and the HCP will report whether the EDD was calculated based on LMP, ultrasound, or ART data. If ultrasound-based, it will also be recorded whether the ultrasound was performed at $<14^{0/7}$, $14^{0/7}$ to $21^{6/7}$, or $\geq 22^{0/7}$ gestational weeks. EDD data will be collected on each data-collection form throughout pregnancy. If the HCP reports a corrected EDD on subsequent forms that is different from the EDD initially reported, the registry will evaluate whether a correction is appropriate (based on the timing of the correction and the methods used to determine the corrected EDD) and follow-up with the HCP, if needed.

The registry will conform to ACOG recommendations for determining the "best" EDD, and EDD will be used to calculate gestational age. Based on the EDD, the following will be calculated:

- First day of LMP, defined as $0^{0/7}$ gestational week, will be calculated as EDD minus 280 days (40 weeks).
- Gestational age will be calculated as the number of weeks elapsed since the first day of LMP.
  - Gestational weeks $0^{0/7}$ to $13^{6/7}$ will be considered the first trimester.
  - Gestational weeks $14^{0/7}$ to $27^{6/7}$ will be considered the second trimester.
  - Gestational weeks $28^{0/7}$ to pregnancy outcome will be considered the third trimester.
- DOC, defined as $2^{0/7}$ gestational weeks, will be calculated as first day of LMP plus 14 days (2 weeks).

If the EDD is not reported by the HCP but LMP data are available, the registry will use the first day of LMP to calculate EDD, gestational age, and DOC.

Individuals will be considered exposed during pregnancy if the exposure occurs any time from 6 months prior to the DOC to the pregnancy outcome. For the analysis of MCM, first trimester exposure will be defined as exposure from 6 months prior to the DOC to $13^{6/7}$ gestational weeks.

9.4. Data sources

9.4.1. Collection of Data on the Electronic Case Report Form

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. The primary data source for this study will be participants self-report and/or the patient's electronic and/or paper medical records. Patients' data obtained from patients, or their HCPs will be recorded on eCRFs. The degree of detail and completeness of data collected is dependent on local clinical practice. See section 9.6 for a detailed description on strategies of data collection.

9.4.2. Registry Awareness, Recruitment, and Retention

9.4.2.1. Participant Recruitment Strategy

An active, targeted, multi-pronged recruitment campaign will be employed to recruit participants for the registry. The campaign will focus on:

- Pregnant individuals
- Patients with MS
- Patients using BRIUMVI™ or other products for the treatment of MS
- Obstetric HCPs
- HCPs who are likely to treat patients with conditions for which BRIUMVI™ may be prescribed
- HCPs who are likely to prescribe BRIUMVI™

Obstetric HCPs and HCPs who are likely to treat patients with conditions for which BRIUMVI™ may be prescribed may be identified via HCP directories and/or professional associations. Pregnant individuals, patients with conditions for which BRIUMVI™ may be prescribed, and patients using BRIUMVI™ may be identified through patient support groups and external data sources, such as pharmacy/medical claims and electronic medical records. The Sponsor's existing infrastructure for distributing BRIUMVI™ and supporting stakeholders (e.g., medical science liaisons/field-facing TG personnel and the patient support program) may be leveraged to identify HCPs who are known to prescribe BRIUMVI™ and pregnant individuals who are using BRIUMVI™.

A multi-modal approach will be used to deliver registry education and recruitment materials to targeted HCPs and patients. This approach involves direct-to-HCP outreach, as well as potential online and print advertising directed to both HCPs and patients. In addition, stakeholders may be identified and provided with information regarding the registry via telephone through the Medical Information Contact Center and the patient support program.

9.4.2.1.1. Direct-to-HCP Outreach

Direct-to-HCP outreach will be achieved by delivering recruitment materials to targeted HCPs via email, fax, and/or hardcopy mail. In addition, the Sponsor's representatives may provide registry education and recruitment materials to HCPs in person. HCPs will be asked to identify

potential registry participants and encourage their participation by speaking to them about the registry and providing them with the patient-directed registry recruitment materials.

9.4.2.1.2. Digital Advertising

Information on the registry and the registry recruitment materials may also be available online. A registry-specific website will be developed, where all recruitment materials will be available for download. The registry website will be discoverable in any internet browser by performing a search related to pregnancy and BRIUMVI™ and/or conditions for which BRIUMVI™ may be prescribed. Information on the registry and/or a link to the registry website will also be available on the following websites:

- FDA listing of pregnancy registries on www.fda.gov, www.clinicaltrials.gov
- PPD website, www.ppd.com/our-solutions/clinical/peri-and-post-approval/non-interventional-studies/pregnancy-and-lactation-studies/

A web-based interface compatible with computers and mobile devices will also be developed to improve information accessibility and enable broader participation. As deemed necessary, online advertisements on social media or other relevant websites (e.g., professional association websites or websites commonly visited by pregnant individuals) may be used to direct potential participants to the registry website.

9.4.2.1.3. Print Advertising

Various print materials will also be used to provide information related to the registry and to facilitate recruitment. The prescribing information for BRIUMVI™ will provide details on the registry, including contact information. Information related to the registry may also be directed to HCPs via announcements/publications in relevant professional journals/newsletters or presentations/exhibits at relevant professional meetings. As deemed necessary, print advertisements in newspapers or magazines with targeted patients among their readership may be used to direct potential participants to the registry, and recruitment materials may be distributed to locations commonly frequented by targeted patients (e.g., ultrasound clinics, gynecologic surgery centers).

9.4.2.1.4. Recruitment Materials

In addition to the registry information in the product label, educational materials designed to elicit interest in registry participation will be developed. All messaging will be aligned with the product label. Materials may include:

- An information sheet and/or brochure that will briefly describe the registry purpose and procedures, including the incentives for participation
- Information on how to access the web-based registry application
- A registration form and sample participant consent form
- The prescribing information (PI)

- Participant consent-to-contact card (this card enables the virtual research coordination center [VRCC] to contact the potential participant and provide additional information about the registry)

9.4.3. Participant Retention Strategy

A retention strategy, facilitated by engaging both the participant and HCP, will seek to minimize the reporting burden on these groups to the extent possible.

The registry staff will serve as the first and single point of communication for registry participants and HCPs. The specialized staff, many of whom are obstetric nurses, have experience collecting data for observational studies from patients and research-naïve HCPs. They are experts at developing a rapport with HCPs and participants to facilitate data collection and build one-on-one relationships that will promote retention and reduce overall loss to follow-up. To encourage HCP engagement, status updates may be shared with HCPs through various means (i.e., email, newsletters, and the registry website). The materials provided will emphasize the mission of the registry to promote participant engagement and point participants to the website.

To reduce the burden of reporting, the registry will use streamlined data-collection processes and simple, concise data-collection forms that focus on the endpoints of interest. The registry will provide multiple options for communication and data submission (e.g., phone, fax, mail, email, website, web-based application), as well as a flexible follow-up schedule to enhance retention and maximize data reporting. The registry will also attempt to collect the contact information of family members or friends if the participant cannot be reached, which can further promote retention.

9.4.4. Assessment of Recruitment and Retention

Participant recruitment and retention are the greatest challenges experienced with pregnancy registries. Recruitment largely depends on a strong awareness campaign and product use or uptake in the market. Low recruitment/enrollment in pregnancy registries may be due to limited use of the product, especially when the product is new to the market. Pregnancy registries typically enroll only a small fraction of all exposed pregnancies, regardless of the awareness strategies employed.

To maximize these processes, the registry's recruitment and retention strategies will be flexible and continuously assessed. The registry will assess recruitment and retention by collecting information from reporters (i.e., HCPs and participating individuals) on the sources from which they received information about the registry (recruitment) and the reasons for which they ceased participation or were lost to follow-up (retention). Based on these assessments, the registry's recruitment and retention strategies will be adjusted to maximize registry participation. The scientific advisory committee (SAC) will also be consulted regarding recruitment and retention strategies (Section 10.4.4).

9.5. Study size

9.5.1. Assessment of Study Feasibility

To assess the feasibility of this study, data-based assumptions regarding the prevalence of MS, pregnancy, and BRIUMVI™ uptake were made to estimate the number of individuals who would potentially be exposed to BRIUMVI™ during pregnancy. The prevalence of MS among individuals of childbearing potential was assumed to be 0.1% (Wallin 2019), the proportion of individuals with RRMS among all individuals with MS was assumed to be 85% (European Medicines Agency 2015), and the proportion of individuals with RRMS receiving pharmacotherapy was assumed to be 95% (as DMTs to slow disease progression are recommended for all patients with RRMS, except those who are pregnant or planning to become pregnant in the near future). It was further assumed that 10% of those receiving pharmacotherapy would be treated with BRIUMVI™. These assumptions were applied to the population of women of childbearing potential in the US (approximately 75 million women aged 15–49 years; US Census 2022), which yielded an estimated 6,056 women of childbearing potential who would potentially receive BRIUMVI™. After application of the general fertility rate in the US (56.0 births per 1,000 women aged 15 to 44 years; Osterman 2022), it was estimated that 339 live births may potentially be exposed to BRIUMVI™ in utero. Given the 3% MCM rate among live births (CDC 2008) in the US general population, these 339 BRIUMVI™ -exposed live births could be expected to result in approximately 10 live births with MCM.

If the registry were to capture one-fourth of the live births exposed to BRIUMVI™ in utero, the registry would be expected to capture approximately 2–3 live births with MCMs.

9.5.2. Sample Size

Table 4 presents the sample size (number of live births or pregnant individuals, depending on the outcome) required in each cohort to detect a relative risk (RR) of 3 for each outcome. Sample size calculations were performed with SAS® statistical software (version 9.4 or higher, SAS Institute, Cary, NC) for the outcomes of interest using the Fisher's exact conditional test with Walters normal approximation method, and assuming a power of 80%, a 2-sided α level of 0.05, an equal number of individuals in each cohort (although other sampling ratios were considered), and observed prevalence rates of the outcomes of interest in the unexposed cohort equivalent to reference comparator rates in the general population. These general population rates were obtained for most (but not all) of the outcomes of interest from various sources, including the MACDP, the National Vital Statistics System (NVSS), the National Institute for Child Health and Human Development's Consecutive Pregnancies Study and Consortium on Safe Labor Study, and published literature.

Although the registry aims to examine a variety of maternal, fetal, and infant outcomes, the target sample size is based on the primary outcome, MCM, which is also the outcome with the most restrictive denominators and one of the lowest prevalence rates in the general population. As shown in Table 4 265 live births in the analysis population of each cohort are needed to detect a 3-fold increase in the prevalence of MCM between cohorts, or an RR of 3. To estimate the number of pregnant individuals who would need to be enrolled to result in 265 live births, several factors were considered, including the expected registry live birth rate, the proportion of

enrolled individuals expected to be exposed to BRIUMVI™ in the first trimester, and the proportion of enrolled individuals expected to be excluded from the analysis population. It was assumed that 90% of enrolled individuals would be exposed in the first trimester, 90% of enrolled pregnancies would result in a live birth (Covington 2010; Veley 2020), and 10% of enrolled individuals would be excluded from the analysis population due to the occurrence of a pregnancy outcome prior to enrollment (retrospectively enrolled participants), exposure to a teratogen or an investigational medication during pregnancy (teratogen/investigational medication-exposed participants), or lack of pregnancy outcome data (participants lost to follow-up). Given these assumptions, to attain 265 live births per cohort, 364 pregnant individuals would need to be enrolled in each of the 2 cohorts of the study population, and a total of 728 individuals would need to be enrolled in the registry. This sample size will afford the study the ability to detect a 3-fold increase in the prevalence of the primary outcome, MCM, in the BRIUMVI™ -exposed cohort, with meaningful confidence (95% confidence level). Additionally, Table 5 shows that, without any adjustments for multiple comparisons, the proposed sample size will afford the study >80% power to detect a 3-fold increase in all other outcomes except eclampsia and stillbirth (for which the study will have 6.3% and 14.35% power to detect a 3-fold increase, respectively).

Table 4: Sample Size Calculations by Outcome

Outcomes	Reference Rate in Non-exposed Group	Reference	Denominator	Sampling Ratio (Exposed: Unexposed)	Sample Size Needed per Cohort to Detect RR = 3.0 (Exposed: Unexposed)
MCM	3.0%	CDC 2008	Live births	1:1	265
Gestational hypertension	6.5%	Butwick 2020	Pregnant individuals	1:1	115
Pre-eclampsia	3.80%	Ananth 2013	Pregnant individuals	1:1	206
Eclampsia	0.3%	Butwick 2020	Live births	1:1	2772
Gestational diabetes	6.9%	Martin 2021	Pregnant individuals	1:1	107
SAB	11.8%	Wu 2019	Pregnant individuals	1:1	57
Stillbirth	0.6%	Gregory 2021	Live births and stillbirths	1:1	1379
Elective termination	18.4%	Jones 2019	Abortions and live births	1:1	31
Preterm birth	8.4%	Osterman 2022	Singleton live births	1:1	85
SGA	10.0%	By definition	Live births	1:1	70
Postnatal growth deficiency	10.0%	By definition	Live births	1:1	70
Infant developmental delay	13.0%	Rosenberg 2008	Live births	1:1	50

Abbreviations: MCM = major congenital malformation; reference rate = prevalence rate of outcome in general population for pregnant individuals of any age; RR = relative risk; SAB = spontaneous abortion; SGA = small for gestational age
Sample size calculations were performed in SAS (version 9.4) for the outcomes of interest using Fisher's exact conditional test with Walters normal approximation method, and assuming a power of 80% and a 2-sided α level of 0.05.

Table 5: Power Calculations

Outcomes	Power Estimate
MCM	80%
Gestational hypertension	> 80%
Pre-eclampsia	>80%
Eclampsia	6.3%
Gestational diabetes	> 80%
SAB	>80%
Stillbirth	14.3%
Elective termination	>80%
Preterm birth	>80%
SGA	>80%
Postnatal growth deficiency	>80%
Infant developmental delay	>80%

Abbreviations: MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small for gestational age

9.6. Data management

9.6.1. Participant Registration

Pregnant individuals who are interested in participating will self-enroll in the registry through the web-based application or by calling the VRCC. To enroll, each individual will answer a series of screening questions to assess her eligibility, and, if eligible, she will be asked to provide informed consent, her primary contact information, alternate contact information for a family member or friend, contact information for HCPs who are/will be involved in her care or the care of her infant, and medical releases to allow these HCPs to provide data to the registry.

9.6.2. Data Collection

Enrolled pregnant individuals and the HCPs involved in their care or the care of their infants, if applicable, will serve as the data reporters to the registry. It is anticipated that most obstetric data will be collected from the pregnant individual's obstetric HCP, defined as any HCP who provides care during pregnancy (e.g., obstetrician, family practitioner, general practitioner), and that most pediatric data will be collected from the infant's pediatric HCP, defined as any HCP who provides pediatric care (e.g., pediatrician, family practitioner, general practitioner). Data may be requested from other HCPs involved in the individual's or infant's care (e.g., prescriber, specialist) after appropriate medical release is obtained.

The data-collection process for each participant will begin at enrollment, and cumulative data throughout the pregnancy will be collected at 3 timepoints: at enrollment, at the end of the

second trimester (approximately 26 gestational weeks), and at pregnancy outcome (live birth or fetal loss). For live-born infants, data from pediatric visits at 4 and 12 months of age will be collected at 2 timepoints: 4 months and 12 months after delivery. Data-collection efforts will be identical for all enrolled pregnant individuals regardless of their exposures and study cohort assignment. HCPs who serve as reporters to the registry will be instructed to transcribe data that are readily available in the patients' medical records into the data-collection forms. The registry will provide multiple options for data reporting (e.g., phone, fax, mail, email, website, web-based application), as well as a flexible follow-up schedule to enhance retention and maximize data reporting.

At enrollment, once consent, registration information (including eligibility criteria), reporter contact information, and medical releases have been provided by the pregnant individual, their maternal demographic characteristics and pre-pregnancy anthropometrics will be collected. These data will be collected on the ***Registration Form for Participants***. Registration information, including eligibility criteria, will be confirmed by HCP(s), as appropriate. The HCP(s) will additionally provide maternal obstetrical history, family history of congenital malformations, disease information, pregnancy information, and maternal exposures during pregnancy. All of these data will be collected on the ***Registration Form for Healthcare Providers and Pregnancy Information Form***. At approximately the end of the second trimester, the HCP(s) will be asked to complete another ***Pregnancy Information Form***, which will collect any updates to pregnancy information and maternal exposures during pregnancy. Around or after the estimated date of delivery (EDD) or after a known pregnancy outcome, the HCP(s) will be asked to complete another ***Pregnancy Information Form***, as well as the ***Pregnancy Outcome Form***, which will collect pregnancy outcome information. For each live-born infant, the pediatric HCP will be asked to complete an ***Infant Outcomes Form***, which will collect infant information, including infant growth and development data, at 2 timepoints: at approximately 4 and 12 months after delivery. These visits are part of the American Academy of Pediatrics' recommended infant well-child visit schedule (American Academy of Pediatrics 2021).

If a congenital malformation (major or minor) or other event of interest is reported, additional information may be requested from the reporting HCP on the ***Targeted Follow-up Form*** to properly characterize the event. On each data-collection form, information regarding the reporter, (i.e., reporter type, name, address, phone, email) and the date that the form was completed will also be collected.

Table 6 provides a summary of the data-collection process, including the forms that will be used to collect the data, the timing for completion of each form, the potential reporters or sources of the data, and the types of data that will be collected. Section 9.6.3 and Section 9.6.4 provides additional details regarding the data collected.

Table 6: Summary of Data Collection Process

Data Collection Form	Data Sources/Reporters	Timing of Completion	Data Collected
Registration Form for Participants	Participant	Enrollment	• Registration information, including eligibility criteria

Data Collection Form	Data Sources/Reporters	Timing of Completion	Data Collected
			• Maternal demographic characteristics • Maternal pre-pregnancy anthropometrics
Registration Form for HCPs	Obstetric HCP and prescriber, if needed	Enrollment	• Registration information, including eligibility criteria • Maternal obstetrical history • Family history of congenital malformations • Disease information • Baseline pregnancy information
Pregnancy Information Form	Obstetric HCP and prescriber, if needed	Enrollment, end of 2nd trimester[a], and EDD/pregnancy outcome[a]	• Ongoing pregnancy information • Maternal exposures during pregnancy
Pregnancy Outcome Form	Obstetric HCP and pediatric HCP, if needed	EDD/pregnancy outcome	Pregnancy outcome information
Infant Outcomes Form	Pediatric HCP	4 and 12 months after delivery	Infant outcome information at 4 and 12 months
Targeted Follow-up Form	Obstetric, pediatric, or other HCP	Any time after pregnancy outcome	Targeted follow-up information

Abbreviations: EDD = estimated date of delivery; HCP = healthcare provider
[a] Obtain updated information since the previous contact.

Registration Information

Collected from participant at enrollment

- Date of first contact with registry
- Date of consent (enrollment)
- Recruitment source(s)
- Minimum data for assignment to a study cohort, including:
  - Pregnancy status
  - MS diagnosis information
  - Exposure information
  - Prior enrollment status (e.g., enrolled in registry with prior pregnancy)

Collected from HCP(s)—obstetric and prescriber, if needed—at enrollment

- Minimum data for assignment to a study cohort, including:
  - Pregnancy status

- MS diagnosis information
- Exposure information

Maternal Demographic Characteristics

Collected from participant at enrollment

- Date of birth
- Ethnicity
- Race
- Education
- Employment status
- Income
- Smoking status and history (e.g., duration and packs per day)
- Alcohol use status and history
- Geographic location

Maternal Pre-pregnancy Anthropometrics

Collected from participant at enrollment

- Pre-pregnancy anthropometrics (weight and height)

Maternal Obstetrical History

Collected from obstetric HCP at enrollment; if not available from HCP, can be collected from participant

- Number of previous pregnancies, including multiple gestations
- Outcomes of previous pregnancies (SAB, stillbirth, elective termination, live birth)
- Complications of previous pregnancies (e.g., pregnancy-induced hypertension, pre-eclampsia, eclampsia, gestational diabetes, preterm labor, placenta previa, placental abruption, incompetent cervix, ectopic pregnancy, molar pregnancy)
- Characteristics of previous live births (preterm, SGA)
- Number of previous fetuses/infants with congenital malformations (major and minor) and contributing factors

Family History of Congenital Malformations

Collected from obstetric HCP at enrollment; if not available from HCP, can be collected from participant

- Maternal and paternal family history of congenital malformations (major and minor) and genetic disorders, including specific malformation and relation of family member to mother or father

Disease Information

Collected from HCP(s) —obstetric and prescriber, if needed—at enrollment

- Maternal history of MS, including date of diagnosis and prior treatments
- Characteristics of MS, including type and severity

Baseline Pregnancy Information

Collected from obstetric HCP at enrollment only

- First day of last menstrual period (LMP)
- Method of conception

Ongoing Pregnancy Information

Collected from obstetric HCP at enrollment, end of 2nd trimester, and pregnancy outcome; at the end of the 2nd trimester and pregnancy outcome, HCPs are asked only for updates to the data previously reported

- Number of fetuses/pregnancy order (i.e., singleton, twin, triplet)
- EDD and method of determination (i.e., LMP, ultrasound, or assisted reproductive technology [ART] data); if ultrasound-determined, timing of ultrasound ($< 14^{0/7}$, $14^{0/7}$ to $21^{6/7}$, or $\geq 22^{0/7}$ gestational weeks)
- Prenatal tests (e.g., ultrasound, amniocentesis, maternal serum alpha-fetoprotein, chorionic villus sampling) performed, including type of test (diagnostic or screening), date of test, and results/findings (e.g., congenital malformations)
- Relevant maternal medical conditions, including, but not limited to:
  - Thyroid abnormalities
  - Obesity
  - Infectious diseases
  - Heart disease
  - Kidney disease
  - Respiratory diseases (e.g., asthma)

  - Diabetes
  - Hypertension
  - Seizure disorder
  - Autoimmune diseases
  - Anemia
  - Depression and other psychiatric disorders
  - Liver diseases (e.g., hepatitis)
  - Sexually transmitted diseases
  - Uterine or cervical abnormalities, including congenital uterine abnormalities
  - Cancer
- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including:
  - Pregnancy-induced hypertension
  - Pre-eclampsia
  - Eclampsia
  - Gestational diabetes
  - Preterm labor
  - Placenta previa
  - Placental abruption
  - Incompetent cervix
  - Ectopic pregnancy
  - Molar pregnancy

Maternal Exposures During Pregnancy

Collected from HCP(s) —obstetric and prescriber, if needed —at enrollment, end of 2nd trimester, and pregnancy outcome; at the end of the 2nd trimester and pregnancy outcome, HCPs are asked only for updates to the data previously reported

- Exposure to BRIUMVI™, including indication/reason for use, dose, route, frequency, and dates/duration of exposure, if available
- Exposure to folic acid and prenatal vitamins, including indication/reason for use, dose, route, frequency, and dates/duration of exposure, if available
- Exposure to other drugs or biological products (including prescription and non-prescription drugs, dietary supplements, vaccines, teratogens, and investigational

medications), including indication/reason for use, dose, route, frequency, and dates/duration of exposure, if available

- Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing of exposure, if available

Pregnancy Outcome Information

Collected from HCP(s) —obstetric and pediatric, if needed—at or after pregnancy outcome

- Pregnancy outcome (for each fetus, classified in 1 of the following mutually exclusive categories: SAB, stillbirth, elective termination, and live birth)
- Date of pregnancy outcome
- Gestational age at pregnancy outcome
- Fetal/infant sex
- Fetal/infant weight, length, and head circumference at pregnancy outcome
- Route of delivery (i.e., spontaneous vaginal delivery, assisted vaginal delivery, or cesarean delivery)
- 5-minute Apgar score
- Congenital malformations (major and minor), including post-mortem findings for fetal losses, if available, and assessment of potential contributing factors
- For a non-induced fetal loss (SAB, stillbirth), factors that may have had an impact on the fetal loss and attribution
- For elective termination, reason (e.g., finding on prenatal test, risk to mother's health, undesired pregnancy)
- Maternal weight at (or just prior to) pregnancy outcome

Infant Outcome Information

Collected from pediatric HCP at 4 and 12 months post-delivery

- Infant weight, length, and head circumference at birth (if not provided at pregnancy outcome) and at 4 and 12 months of age
- Achievement of the developmental milestones in each Centers for Disease Control and Prevention (CDC)-defined category (social/emotional, language/communication, cognitive, and movement/physical development) at 4 and 12 months of age
- Congenital malformations (major and minor) and assessment of potential contributing factors
- Infant illnesses/medical conditions (e.g., B cell depletion), including start and end dates and description

- Infant infections, including date of onset, severity, type, site, causative organism, attribution, treatment, and outcome of each infection
- Infant hospitalizations, including start and end dates, reason for hospitalization, and treatments received
- Infant death, including date and cause of death

Targeted Follow-up Information

Collected from HCP(s) —obstetric and/or pediatric—at any time after pregnancy outcome

- Details of congenital malformations (major or minor) or other conditions of interest
- Etiology
- Outcome attribution
- Specific questions requested by the Sponsor and/or the birth defect evaluator

9.6.3. Attempts to Obtain Follow-up Information

In the month that the follow-up is due, the HCP will be contacted and asked to provide follow-up information. If needed, 3 subsequent attempts will be made approximately every 2 weeks via various modes of communication. If no response is received from the HCP, additional attempts may occur at the next planned data-collection timepoint (e.g., at pregnancy outcome). When appropriate, the participant will be asked to encourage her HCP to provide the missing data. A final communication to obtain follow-up data will be sent via certified mail indicating that the participant will be considered lost to follow-up if no further data are received. If, at any point in the follow-up process, the participant withdraws consent or the HCP indicates that the participant is lost to follow-up, no further communication attempts will be made. The reason the participant was lost to follow-up (e.g., no response from HCP, no response from participant, or participant withdrawal of consent) will be documented.

9.6.4. Follow-up Process for Clarification of Information

For critical data points (e.g., exposure and outcome data), if there are outstanding questions, discrepancies between forms, or missing data, the appropriate HCP will be contacted for clarification. If needed, 3 subsequent attempts will be made at intervals of approximately 2 weeks. If no further information is obtained, qualified registry staff or the principal investigator will make a logical determination on discrepant information based on the available data. All clarifications and/or changes will be documented and traceable.

9.6.5. Registry Participant Management and Disposition

9.6.5.1. Valid Versus Invalid Participants

A valid participant is defined as a pregnant individual with sufficient data that is submitted or confirmed by an HCP for determining inclusion/exclusion into one of the study population cohorts (Section 9.2.2.1). Participants who lack the minimum data required for determining

inclusion/exclusion into one of the study cohorts or who lack confirmation from an HCP will be considered invalid. Invalid participants will be enumerated in each registry report but will not be included in statistical analyses.

9.6.5.2. Prospectively Enrolled Versus Retrospectively Enrolled Participants

Prospective registration will be encouraged with the registry; however, retrospective enrollment in the registry will be permitted as well. A prospectively enrolled participant is defined as a pregnant individual who enrolls prior to the pregnancy outcome. A retrospectively enrolled participant is defined as a pregnant individual who enrolls after the pregnancy outcome has occurred.

Retrospectively enrolled participants can introduce bias toward the reporting of more unusual and severe outcomes and are less likely to be representative of the general population than prospectively enrolled participants. Therefore, retrospectively enrolled participants will be excluded from the analysis population but will be included in supplementary analyses.

Diagnostic prenatal tests (e.g., ultrasound to scan for structural defects at approximately 20 gestational weeks, chorionic villus sampling, and amniocentesis) can determine with high accuracy whether a fetus has a structural or chromosomal abnormality. Therefore, inclusion of individuals who have had diagnostic prenatal testing in the analysis population may introduce bias. To examine this potential bias, a sensitivity analysis that applies a stricter definition of prospective enrollment will be conducted. For this analysis, individuals who enroll prior to diagnostic prenatal testing will be considered prospectively enrolled, and individuals who enroll after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled. The outcomes of individuals who enroll prior to diagnostic prenatal testing will be compared with those of individuals who enrolled after diagnostic prenatal testing.

9.6.5.3. Participants Exposed to Teratogens or Investigational Medications

Participants will be considered exposed to teratogens or investigational medications during pregnancy if a dose is taken at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within a specified time period based on the product's half-life). Participants will be considered exposed during pregnancy if a dose is taken prior to conception within a time period equivalent to 5 times the product's half-life. A list of teratogens (Annex 3) has been developed and will be continually updated based on the data available in the Teratogen Information System (TERIS) database of teratogenic agents and publications (Feldkamp 2015; Polifka 2002; TERIS 2021; Zomerdijk 2015). Participants who are exposed to teratogens or investigational medications during pregnancy will be excluded from the analysis population but will be included in supplementary analyses.

9.6.5.4. Participants Exposed to Other Anti-CD20 Monoclonal Antibodies

To avoid confounding by medication class effect, individuals who are exposed to anti-CD20 monoclonal antibodies will be excluded from enrollment and analyses, as appropriate. Individuals exposed to anti-CD20 monoclonal antibodies other than BRIUMVI™ during pregnancy and prior to study enrollment will not be permitted to enroll. Women who are enrolled

but later exposed to other anti-CD 20 monoclonal antibodies will be excluded from the analysis population; however, these participants will be analyzed in supplementary analyses.

9.6.5.5. Participants Lost to Follow-up

A participant will be considered lost to follow-up if follow-up information is never obtained or is unavailable; pregnant individuals without pregnancy outcome information and live-born infants without follow-up data after birth will be considered lost to follow-up. Section 9.6.3 provides more information on the circumstances under which participants will be considered lost to follow-up. Information from these participants (e.g., baseline characteristics, abnormal prenatal test results, and reason for loss to follow-up, if available) will be summarized in each registry report, but these participants will be excluded from the analysis population.

9.6.5.6. Subsequent Pregnancies

Individuals who have previously enrolled in the registry with a prior pregnancy will be eligible to enroll in the registry with subsequent pregnancies and will be included in the analysis population. Statistical non-independence due to multiple pregnancies from the same individual will be addressed in the analysis.

9.6.5.7. Multiple-gestation Pregnancies

Multiple-gestation pregnancies will be enrolled in the registry and included in the analysis population; however, for the analyses of preterm birth, SGA, and postnatal growth deficiency, multiple-gestation pregnancies will be excluded from the analysis population due to the higher risk of these outcomes in twins and higher-order multiples.

9.6.5.8. Analysis Population

The analysis population will include participants who:

- Are valid (Section 9.6.5.1)
- Are prospectively enrolled (Section 9.6.5.2)
- Are not exposed to teratogens or investigational medications during pregnancy (Section 9.6.5.3)
- Are not considered lost to follow-up (Section 9.6.5.5)

For the analyses of preterm birth, SGA, and postnatal growth deficiency, multiple-gestation pregnancies will be excluded from the analysis population (Section 9.6.5.7).

9.7. Data analysis

9.7.1. Methods of Analysis

Analyses will be conducted in accordance with the study objectives, statistical analysis plan (SAP), table/listing/figure shells, and applicable guidelines.

Registry data will be summarized in tables, listings, and figures by study cohort, as appropriate. These data include maternal demographic characteristics and pre-pregnancy anthropometrics,

pregnancy information, maternal obstetrical history, family history of congenital malformations, disease information, maternal exposures during pregnancy, pregnancy outcome information (including gestational age of outcome), and infant outcome information. For each continuous variable, the number of observations, median, mean, standard deviation, minimum, and maximum will be reported. For each categorical variable, the frequency and percentage in each category will be reported. The frequency and percentage of subjects with missing data for each data point will be presented. Results will be rounded to 1 decimal place; therefore, percentages may not always add up to 100.

The demographic and baseline characteristics, and prevalence rates of the outcomes of interest will be compared between the study cohorts. Comparisons will be conducted using the methods described below, and 95% confidence intervals will be reported, as appropriate, to reflect statistical uncertainty.

Data analyses will be performed with SAS statistical software (version 9.4 or higher, SAS Institute, Cary, NC). Additional details will be provided in the SAP.

9.7.1.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics, and balance between cohorts will be assessed using standardized differences. These data will be presented before and after balancing using the inverse probability weighting (IPW) method (Section 9.7.2.4). In addition, within each cohort, those included in the analysis population will be compared with those excluded from the analysis population for being lost to follow-up, retrospectively enrolled, or exposed to teratogens or investigational medications during pregnancy.

9.7.2. Analysis of the Outcome Measures

For the primary analysis, pregnancy outcomes will be compared between the exposed and unexposed cohorts using the analysis population. Supplementary analyses will be conducted that additionally include individuals who were excluded from the primary analysis. Where sample size permits, subgroup analyses will be conducted that consider the timing and extent of exposure, and maternal age group at conception. Sensitivity analyses will also be conducted to examine the extent to which changes in certain methods or assumptions affect the results.

9.7.2.1. Comparison with Internal Comparator Cohort

Formal quantitative comparisons of prevalence rates of the outcomes of interest will be conducted between the exposed and unexposed cohorts. The prevalence rates of the outcomes of interest will be calculated as described in Section 9.7.2.3.

For each outcome, if the number of events permits, results will be presented for both unadjusted and adjusted models. RRs will be reported along with their 95% confidence intervals. Exact methods will be used to calculate crude (unadjusted) RRs for all outcomes.

Adjusted methods will incorporate weights estimated using the IPW method to balance the cohorts with regard to observable covariates (Section 9.7.2.4). For each outcome, a weighted generalized linear model using a binomial family and a log (RR) link will be employed to

estimate an adjusted RR. The adjusted comparison of the prevalence rates of MCMs observed in the exposed and unexposed cohorts will be considered the primary analysis.

9.7.2.2. Comparison With External Comparators

Analyses will also be conducted to compare the prevalence rates of the outcomes of interest among exposed participants of the main analysis population with those of selected external comparators (e.g., MACDP, NVSS), if available. The prevalence rates of the outcomes of interest will be calculated as described in Section 9.7.2.3. These registry prevalence rates will then be compared with those of selected external comparators using Exact methods. Prevalence rates will be reported along with their 95% CIs and p-values for the comparison.

9.7.2.3. Calculation of Outcome Prevalence

Prevalence rates of the outcomes of interest will be calculated according to the conventions described in Table 7. In general, the prevalence of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome, based on clinical knowledge. Prevalence is preferred over incidence when examining pregnancy outcomes, such as congenital malformations, because incidence cannot be reliably estimated given the complexities in the reproductive process (Mason 2005).

For most outcomes, the analysis population (denominator) will be the number of pregnancies with pregnancy outcome data, the number of live births, or the number of infants with follow-up data at the timepoint of interest, as appropriate; however, for some outcomes, the analysis population (denominator) will be restricted based on certain relevant factors:

- For MCM, prevalence in the exposed cohort will be calculated among the subset of pregnancies exposed during the first trimester.
- For MCM, prevalence will be calculated among live births for the primary analysis, and a secondary analysis will be conducted among live births and fetal losses.
- For preterm birth, SGA, and postnatal growth deficiency, prevalence will be calculated among singleton live births due to the higher risk of these outcomes in twins and higher-order multiples.
- For live birth and infant outcomes (i.e., preterm birth, SGA, postnatal growth deficiency, and infant developmental delay), prevalence will be calculated among live births/infants without MCMs.
- For postnatal growth deficiency, infants born preterm or SGA will be excluded from the analysis population (denominator).
- For infant developmental delay, infants born preterm will be excluded from the analysis population (denominator).
- For SAB and preterm birth, prevalence will be calculated among the subset of pregnancies enrolled in the registry prior to 20 and 37 gestational weeks, respectively.
- For some outcomes, prevalence will be calculated at multiple timepoints. For example, postnatal growth deficiency and infant developmental delay will be assessed

at 4 and 12 months of infant age. At each timepoint, prevalence will be calculated among infants with data available for the particular outcome at that timepoint.

For comparison with external comparators, the prevalence rates of the outcomes of interest among the exposed participants of the analysis population will be calculated according to the conventions used by the selected external comparators. For example, for the comparison with MACDP, live births and stillbirths with MCMs, including MCMs not associated with medication exposure, will be included in the numerator, and the denominator will be the number of live births. The MACDP calculates rates by this convention, which increases sensitivity.

Table 7: Calculation of Outcome Prevalence

Outcome	Numerator	Denominator
Primary Outcome – MCM		
Primary analysis between internal cohorts: Among live births	Live births with confirmed MCMs (excluding MCMs not associated with medication exposure) among pregnancies with pregnancy outcome data and, if applicable, exposure during 1st trimester	Live births among pregnancies with pregnancy outcome data and, if applicable, exposure during 1st trimester
Secondary analysis between internal cohorts: Among all pregnancy outcomes	Live births and fetal losses with confirmed MCMs (excluding MCMs not associated with medication exposure) among pregnancies with pregnancy outcome data and, if applicable, exposure during 1st trimester	Live births and fetal losses among pregnancies with pregnancy outcome data and, if applicable, exposure during 1st trimester
Comparison with external comparator (CDC MACDP)	Live births and stillbirths with confirmed MCMs (including MCMs not associated with medication exposure) among pregnancies with pregnancy outcome data and exposure during the 1st trimester	Live births among pregnancies with pregnancy outcome data and exposure during the 1st trimester
Secondary Outcomes		
Minor congenital malformations	Live births with minor congenital malformations among pregnancies with pregnancy outcome data	Live births among pregnancies with pregnancy outcome data
Gestational hypertension		
Primary analysis between internal cohorts	Gestational hypertension among pregnancies with pregnancy outcome data	Pregnancies with maternal pregnancy complications data
Comparison with external comparator (US Birth Certificate Data)	Gestational hypertension among live births	Live births among pregnancies with pregnancy outcome data
Pre-eclampsia	Pre-eclampsia among pregnancies with pregnancy outcome data	Pregnancies with maternal pregnancy complications data
Eclampsia		
Primary analysis between internal cohorts	Eclampsia among pregnancies with pregnancy outcome data	Pregnancies with maternal pregnancy complications data

Outcome	Numerator	Denominator
Comparison with external comparator (US Birth Certificate Data)	Eclampsia among live births	Live births among pregnancies with pregnancy outcome data and maternal pregnancy complications data
Gestational diabetes		
Primary analysis between internal cohorts	Gestational diabetes among pregnancies with pregnancy outcome data	Pregnancies with maternal pregnancy complications data
Comparison with external comparator (CDC NVSS)	Gestational diabetes among live births	Live births among pregnancies with pregnancy outcome data and maternal pregnancy complications data
SAB	SABs among pregnancies with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 20 gestational weeks	Pregnancies with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 20 gestational weeks
Stillbirth		
Primary analysis between internal cohorts: among all pregnancy outcomes	Stillbirths among pregnancies with pregnancy outcome data	Pregnancies with pregnancy outcome data
Comparison with external comparator (CDC NVSS)	Stillbirths among pregnancies with pregnancy outcome data	Live births and stillbirths among pregnancies with pregnancy outcome data
Elective termination		
Primary analysis between internal cohorts: among all pregnancy outcomes	Elective terminations among pregnancies with pregnancy outcome data	Pregnancies with pregnancy outcome data
Comparison with external comparator (Guttmacher Institute)	Elective terminations among live births and abortions	Live births and abortions among pregnancies with pregnancy outcome data
Preterm birth	Singleton preterm live births without MCMs among pregnancies with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 37 gestational weeks	Singleton live births without MCMs among pregnancies with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 37 gestational weeks
SGA	Singleton live births without MCMs who are SGA among pregnancies with pregnancy outcome data	Singleton live births without MCMs with weight data among pregnancies with pregnancy outcome data
Postnatal growth deficiency (at 4 and 12 months)	Singleton infants without MCMs who were not born preterm or SGA with postnatal growth deficiency based on weight/length/head circumference among infants with weight/length/head circumference data at the timepoint	Singleton infants without MCMs who were not born preterm or SGA with weight/length/head circumference data at the timepoint

Outcome	Numerator	Denominator
Infant developmental delay (at 4 and 12 months)	Infants without MCMs who were not born preterm with developmental deficiency in a particular category among infants with developmental milestone data for the category at the timepoint	Infants without MCMs who were not born preterm with developmental milestone data for the category at the timepoint
Infant serious or opportunistic infections	Infants with a qualifying infection from birth to 1 year of age among infants with infection data up to 1 year of age	Infants with infection data up to 1 year of age
Infant hospitalizations	Infants with a qualifying hospitalization from birth to 1 year of age among infants with hospitalization data up to 1 year of age	Infants with hospitalization data up to 1 year of age

Abbreviations: MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small for gestational age

9.7.2.4. Adjustment for Covariates and Confounders

Because of the real-world nature of the study, there is a high potential for imbalance between the cohorts with regard to observed covariates. To address this imbalance, adjusted analyses that employ the IPW method will be conducted. The IPW method is widely used in observational studies, and, unlike propensity score matching, the IPW method does not require a 1:1 match between participants in the 2 cohorts being compared (Robins 1994; Robins 1995; Scharfstein 1999).

The IPW approach assigns a weight to each participant based on observed covariates; the weight is equivalent to the inverse probability of the participant belonging in her assigned cohort (inverse propensity score). Weights will be estimated for each participant using logistic regression, then the weights will be incorporated into a regression model to balance the cohorts. When cohorts are far from being balanced, extreme weights can affect the results. Stabilized weights are thus preferred and will be applied.

All potential confounders (see Section 9.7.2.5) will be considered for inclusion in the logistic regression model used to calculate weights (propensity score model). Covariate data measured post-exposure will not be included in the weighted outcome model, since incorporating covariates after exposure may undermine the causal framework and potentially lead to biased estimates. A high rate of missing data for a covariate could make application of the IPW method more challenging, as weights can be estimated only for participants with known values. If there is a high degree of missing covariate data and multiple imputation is applied, the imputed values will be used for weight estimation.

If imbalances between the cohorts remain after weighting, models may be further adjusted using direct adjustment for additional covariates, if the number of events permits. The final selection of covariates will depend primarily on data availability and clinical guidance, not data-driven methods. The list of covariates and confounders will be considered for each outcome separately. The final selection will be driven by clinical importance and by observed imbalances in the model. As the expected frequency of outcomes in the study is small, the number of potential covariates included in the model could be limited. Priority will be given to covariates that are possibly associated with the exposure and outcomes.

9.7.2.5. Potential Covariates and Confounders

In accordance with the FDA and the Agency for Healthcare Research and Quality (AHRQ) guidance (FDA 2019; Gliklich 2020), the following potential covariates and confounders may be included in multivariable analyses, as appropriate:

- Maternal age at conception
- Calendar year at conception
- Maternal race
- Maternal ethnicity
- Proxies for maternal socioeconomic status, including maternal education, employment status, and income
- Smoking history prior to pregnancy
- Alcohol use history prior to pregnancy
- Geographic region
- Maternal pre-pregnancy body mass index, calculated from pre-pregnancy weight and height
- Gestational age at registry enrollment
- Method of conception
- Number of fetuses/pregnancy order
- Pre-BRIUMVI™ exposure maternal medical conditions, including thyroid abnormalities, obesity, infectious diseases, heart disease, kidney disease, respiratory diseases (e.g., asthma), diabetes, hypertension, seizure disorder, autoimmune diseases, depression and other psychiatric disorders, liver diseases (e.g., hepatitis), sexually transmitted diseases, cancer, and uterine or cervical abnormalities (e.g., congenital uterine abnormalities) (for current pregnancy)
- Pre-BRIUMVI™ exposure pregnancy related maternal medical conditions or pregnancy complications, including pregnancy induced hypertension, pre eclampsia, eclampsia, gestational diabetes, preterm labor, placenta previa, placental abruption, incompetent cervix, ectopic pregnancy, and molar pregnancy
- Number of previous pregnancies
- Previous pregnancy outcomes (SAB, stillbirth, elective termination, live birth)
- Previous pregnancy complications
- Characteristics of previous live births (preterm, SGA)
- Previous fetus/infant with congenital malformations (major and minor)
- Family history of congenital malformations (major and minor)
- Characteristics of MS, including type, severity, and duration

- Pre-BRIUMVI™ exposure maternal use of folic acid during current pregnancy and gestational age at exposure
- Pre-BRIUMVI™ exposure maternal use of prenatal vitamins during pregnancy and gestational age at exposure
- Pre-BRIUMVI™ exposure maternal use of other drugs or biological products, including prescription and non prescription drugs, dietary supplements, and vaccines, during pregnancy and gestational age at exposure
- Pre-BRIUMVI™ exposure maternal use of tobacco, alcohol, marijuana, and recreational or illicit drugs during pregnancy and frequency and timing of exposure
- Maternal weight gain during pregnancy

9.7.2.6. Subgroup Analyses

Where sample size permits, subgroup analyses will be conducted for all outcomes that consider:

- Timing of exposure (earliest trimester of exposure, all trimesters of exposure)
  - Trimesters will be categorized as described in Section 9.3.4
  - Preconception exposure window will be further categorized as follows: 4 to 6 months preconception, 2 to <4 months preconception, and DOC+1 day to <2 months preconception
- Extent of exposure (cumulative dose during pregnancy or relevant exposure window)
- Maternal age group at conception (<18, 18 to <35, 35 to <45, and ≥45 years)

The analysis of MCMs will be stratified by:

- Earliest trimester of exposure, with a primary focus on exposure during the first trimester
- System organ class of the defect

9.7.2.7. Supplementary Analyses

Supplementary analyses will be conducted that include pregnant individuals who were excluded from the analysis population due to:

- Occurrence of the pregnancy outcome prior to enrollment (retrospectively enrolled participants)
- Exposure to a teratogen or an investigational medication during or prior to pregnancy (teratogen/investigational medication-exposed participants)

9.7.2.8. Sensitivity Analyses

Sensitivity analyses will also be conducted to examine the extent to which changes in certain methods or assumptions affect the results.

As described in Section 9.6.5.2 , a sensitivity analysis of MCMs will be conducted that applies a stricter definition of prospective enrollment. For this analysis, individuals who enroll prior to diagnostic prenatal testing will be considered prospectively enrolled, and individuals who enroll after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled. The outcomes of individuals who enroll prior to diagnostic prenatal testing will be compared with those of individuals who enrolled after diagnostic prenatal testing.

To assess potential confounding by indication, a sensitivity analysis will be conducted that excludes individuals with MS who are not exposed to any products for the treatment of MS from the unexposed internal cohort. For this analysis, the outcomes of individuals with MS exposed to BRIUMVI™ will be compared with those of individuals with MS who are exposed to other products for the treatment of MS. If sufficient numbers are observed, a subgroup analysis will be performed by exposure to no MS treatments to compare the outcomes of individuals with MS exposed to BRIUMVI™ with those of individuals with MS who are not exposed to any other products for the treatment of MS.

Separate sensitivity analyses may also be conducted to assess the potential impact of missing data, if the rate of missingness is high; details will be provided in the SAP.

9.7.3. Missing Data

A prospective pregnancy cohort study involves an efficient and structured data collection process. As a result, the report burden is minimal and results in a high level of completeness for exposure and outcome data. Therefore, for critical data points, missing values are expected to be minimal, thereby negating the need for imputation. As described in Section 9.6.3, the registry will make multiple attempts to obtain missing data for critical data points. The frequency and percentage of subjects with missing data for each data point will be presented.

For the start and end dates of medical conditions or exposures, if the month and year are known but the day is missing, then the day will be imputed for analyses: missing start dates will be set to the first day of the month, and missing end dates will be set to the last day of the month. Listings will continue to present the day as missing.

In the propensity model for weight estimation, missingness indicators will be included if the degree of missingness for a particular covariate is not extreme (El-Masri 2005). Although unlikely, if there is a high degree of missingness for a particular covariate (>30%), the covariate will be removed from the model (El-Masri 2005).

If there is a high degree of missing covariate data, further imputation (e.g., multiple imputation using fully conditional specification, also known as imputation by chained equations or sequential generalized regression) may be considered to minimize the loss of observations in the analysis. Further details will be provided in the SAP.

9.8. Quality control

9.8.1. Administrative Procedures

9.8.1.1. Quality Assurance

Ensuring that the data obtained and delivered to the Sponsor are of high quality will be an ongoing, multistep process involving programming of edit checks for critical data variables in the electronic data capture system and visual review for completeness, logic, consistency, and accuracy. As is recommended in regulatory guidance documents, data-collection forms have been carefully designed to ensure data quality and integrity. Participant-reported data may be verified by the appropriate HCP. PPD will follow their SOPs as they relate to the training of personnel, data handling, and processing, complying with 21 CFR Part II and GPP.

Sections 9.6.2, 9.6.3, and 9.6.4further describe processes to ensure complete and accurate data collection for the study.

9.8.1.2. Study Funding

TG Therapeutics, Inc. is the Sponsor of the study and is funding the study.

9.8.1.3. External Contract Organizations

PPD will be responsible for the conduct and administrative aspects of the study.

9.8.1.4. Study Closure

In accordance with industry guidance (FDA 2019), the registry could consider discontinuation in any of the following circumstances:

- Information sufficient to meet the scientific objectives of the registry accumulates
- Other methods of gathering appropriate information become achievable or are deemed preferable
- The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or losses to follow-up

Prior to discontinuation of this registry, regulatory authorities will be consulted, as appropriate.

9.8.1.5. Retention of Study Data

Investigators must retain all study records required by the Sponsor and by the applicable regulations in a secure and safe facility. The investigator must consult a Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained for a period of 15 years after close of the registry in accordance with PPD policies. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.9. Limitations of the research methods

The general limitations of pregnancy registries with voluntary participation are well known, and these will apply to this study as well. One key limitation of the study is the limited size of the population of pregnant individuals expected to be exposed to BRIUMVI™ during pregnancy.

Another key limitation of the registry, due to the voluntary nature of participation, relates to representativeness. Since participation in the registry is voluntary, the pregnant individuals who voluntarily enroll in the registry may not be representative of the overall target population of pregnant individuals with MS in the US. This could introduce selection bias and affect the generalizability of the results. To minimize the potential for selection bias, a multi-faceted recruitment strategy will be employed.

Because the registry will enroll individuals only after recognition of pregnancy, and in some cases, much later in pregnancy, there will be left truncation of the enrolled population. That is, the enrolled population of pregnant individuals will include individuals with a shortened period at risk of the outcomes of interest and exclude individuals who have already had certain outcomes (e.g., SAB, elective termination). To minimize the impact of this potential bias, statistical methods may be used to address left truncation, and the registry's recruitment strategy will encourage recruitment of participants as early in pregnancy as possible.

Additionally, individuals in the exposed cohort may differ from those in the unexposed cohort with regards to important factors that could impact pregnancy outcomes. To minimize the impact of potential confounders, the registry will record the characteristics of individuals in both cohorts and use statistical methods to examine and account for any differences between cohorts in the analysis. The registry will employ identical data-collection and follow-up procedures across the registry cohorts to minimize any potential bias. Although statistical methods will be used to account for confounding or mediating variables, it may not be possible to control for all variables (e.g., unknown) that could influence the results of the study. Therefore, some important confounders (either measured or not) could still be unbalanced.

As described in Section 9.7.1, comparisons of prevalence rates of the outcomes of interest will be conducted between the exposed and unexposed cohorts. The adjusted comparison of the prevalence rates of MCMs observed in the exposed and unexposed cohorts will be considered the primary analysis. Because patients who seek and receive pharmacotherapy for conditions for which BRIUMVI™ may be prescribed may have greater disease severity, confounding by indication (also known as channeling bias) will need to be carefully considered for this comparison. Confounding by indication can occur when patient characteristics, such as disease severity, affect prescribing patterns. If not accounted for in the analysis, such confounding could result in an apparent increased risk of the outcomes of interest associated with medication use. As is described in Section 9.7.2.4, this study will employ the IPW method to address the imbalance between cohorts; however, if the cohorts vary greatly in terms of disease severity, this comparison may nonetheless fail to produce meaningful results.

Since the registry is focused on prospective enrollment, misclassification of drug exposure is non-differential with regard to outcome. However, outcome misclassification could occur, especially with regard to minor congenital malformations that may be overlooked or unreported. Although some MCMs may not be easily visible at birth, most will be apparent by 12 months of

age, so misclassification of these outcomes is expected to be minimal in this registry, which aims to follow infants through 12 months of age.

It is possible that outcomes among pregnant individuals and infants lost to follow-up could differ from those with documented outcomes. Because of differences in individual reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases from the losses to follow-up may have on the analyses. However, the characteristics of those participants considered lost to follow-up will be descriptively compared with those in the analysis population in an attempt to address this potential source of bias.

Pregnancies that result in fetal losses (stillbirths, SABs, and elective terminations) without reported MCMs may introduce a classification bias. The percentage of these pregnancies consisting of potentially normal outcomes or MCMs is unknown. The data-collection form will attempt to obtain information on MCMs detected at the time of the outcome; however, the reporting HCP may not know the condition of the lost fetus.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

The Sponsor respects the participants' rights to privacy and will ensure the confidentiality of their medical information in accordance with applicable laws and regulations. Each participant's identity will be known only to the third-party contractor (i.e., PPD), the central registry site (principal investigator, medical monitor, and VRCC), and the enrolling/participating individual (i.e., patient or HCP). At no time during the operation of the registry will the Sponsor have access to personal identifier information for any individual or any infant who has been enrolled in the registry, with the exception of date of birth for safety reporting purposes. The registry will assign all individuals and infants identification numbers, which will be used to identify registry participants and their infant offspring. The dataset used in each analysis of data from the registry will contain coded registry participant identifiers only for the pregnant individuals and infants.

Each employee in the VRCC is fully trained in the protection of human subjects and data privacy, and follows established standard operating procedures (SOPs) that specifically outline how to maintain confidentially of and data protection for all registry participants. These SOPs also establish procedures should privacy be compromised in any way. The VRCC staff must train and test on these privacy SOPs annually.

10.1. Exemption of Health Insurance Portability and Accountability Act Authorization

As a post-marketing safety reporting activity, this registry meets the following criteria and is therefore exempt from the US Health Insurance Portability and Accountability Act (HIPAA) authorization.

The Code of Federal Regulations (CFR), in 45 CFR 164.512, states:

> (iii) A person subject to the jurisdiction of the Food and Drug Administration (FDA) with respect to an FDA-regulated product or activity for which that person has responsibility, for the purpose of activities related to the quality, safety or effectiveness of such FDA-regulated product or activity. Such purposes include:
>
> a. To collect or report AEs (or similar activities with respect to food or dietary supplements), product defects or problems (including problems with the use or labeling of a product), or biological product deviations;
> b. To track FDA-regulated products;
> c. To enable product recalls, repairs, or replacement, or lookback (including locating and notifying individuals who have received products that have been recalled, withdrawn, or are the subject of lookback); or
> d. To conduct post marketing surveillance.

To further clarify this issue, an article published by the Pregnancy Labeling Task Force, US FDA, states:

> The HIPAA Privacy Rule specifically permits the disclosure of protected health information by covered entities such as physicians or hospitals for public health purposes related to the quality, effectiveness and safety of FDA-regulated products to both the manufacturers and directly to the FDA. This includes collecting or reporting AEs, tracking FDA-regulated

products and conducting post-marketing surveillance to comply with requirements or at the direction of the FDA (Kennedy 2004).

10.2. Informed Consent

Informed consent will be obtained for each registry participant. Electronic consent will be available through the web-based registry application. Should participants prefer to enroll via phone, this registry qualifies for a waiver of documentation of informed consent. Adult participants will be given the option to provide verbal consent under the waiver of documentation of informed consent, or signed informed consent through the web-based application or via courier. Adults are defined as individuals who have attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various states within the US.

Minors are defined as individuals who have not attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various states within the US. The definitions of a minor and an emancipated minor vary by state within the US. This registry will follow applicable laws for the state in which the participant resides. If a minor requests participation in the registry and all eligibility criteria are met, the registry will obtain assent from the minor and signed written consent from a parent or guardian through the web-based application or via courier. Written consent from parent(s) or both guardian(s) will be obtained in the US states in which this is required by local laws and regulations.

At the initial screening with potential participants, consent will be obtained by the web-based registry application or a registry associate to collect basic information about the individual, such as age and state of residence, to determine whether the individual is a minor and to ensure that applicable local laws and regulations are followed.

10.2.1. Additional Safeguards for Children in Clinical Investigations

Although this registry involves the collection of information on infants after birth, the registry protocol will be conducted in full consideration of 21 CFR Part 50, Subpart D, Additional Safeguards for Children in Clinical Investigations (for FDA-regulated human subjects research). This registry will ascertain maternal and infant information only via maternal and pediatric HCPs, and no clinical specimens will be collected from the infants; therefore, data collected on infants of individuals in this pregnancy registry involves no greater than minimal risk to the infants. Although the infants will be too young to provide assent, the registry protocol will require permission from the mothers, and they will be asked to provide authorization for release of medical information from their infants' HCPs.

10.2.2. Electronic Informed Consent Process

The website will contain information about the registry and will provide access to the web-based registry application. Using the web-based application, the individual will register with her computer or mobile device with credentials (i.e., name, email address, and password).

Once the individual has registered, the application will automatically start the consent process. The application will present the contents of the consent form in a scrollable window. The

individual will review the document, and the application will present the following options: "Hold," "Disagree," and "Sign and Publish."

If the individual has questions during the consent process, she will be encouraged to stop the consenting process on the application via the "Hold" button and call the VRCC, where study specialists will assist with any questions. The individual can resume completion of the consent process at any time. If the individual does not wish to provide consent, she will be directed to choose the "Disagree" option, and the process will stop. If the individual wishes to provide consent, she will be directed to choose "Sign and Publish."

The application will provide an option for the individual to view or email her completed consent form(s).

After the informed consent form is complete, the individual will complete the medical release form(s) and answer some basic medical information questions.

Country-specific laws and regulations will be followed if the registry is expanded to other countries.

10.2.3. Waiver of Documentation of Informed Consent

The following US regulations indicate that waiver of documentation of informed consent is appropriate for this registry.

As is stated in US CFR, 21 CFR 56.109 (and additionally in 45 CFR 46.117(c)(2)):

> (c) An IRB shall require documentation of informed consent in accordance with 50.27 of this chapter, except as follows:
>
> > (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context
>
> (d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

The research involves no more than minimal risk to the participants. This is an observational study that involves no experimental intervention and poses no possibility of physical harm. The only potential risk is a breach of confidentiality, and the registry has well-established procedures in place to prevent any such breach. Extensive safeguards are in place to ensure that participants' privacy is protected:

a. An adequate plan is provided to protect the identifiers from improper use and disclosure (Section 10).
b. An adequate plan is provided to remove the identifiers at the earliest opportunity.
c. Adequate assurances are provided that the protected health information will not be reused or disclosed to any other person or entity.

The research involves no procedures for which written consent is normally required outside the research context. Enrollment in this observational study will be strictly voluntary,

and participants can withdraw their consent to participate at any time. The schedule of patient visits and all treatment regimens will be at the discretion of the treating HCP. Data submitted to the registry will be limited to data routinely collected and documented in the patient's medical record.

10.3. Regulatory and Ethical Compliance

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) (GPP 2015), with applicable local regulations and with the ethical principles established in the Declaration of Helsinki. The protocol will be submitted to the applicable regulatory authority and central IRB for approval prior to registry implementation. The protocol, waiver of documentation of informed consent, and waiver of informed consent will be reviewed and approved by an IRB before study implementation. A signed and dated statement that the protocol and waivers have been approved by the IRB will be given to the Sponsor before study initiation. Prior to study start, the investigator will sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol. If an inspection of the site is requested by a regulatory authority, the investigator must inform the Sponsor immediately that this request has been made.

10.4. Roles and Responsibilities of the Sponsor, Principal Investigator, Co-Investigators, Scientific Advisory Committee, and Virtual Research Coordination Center

The Sponsor and the principal investigator will comply with this protocol and applicable regulations and ethical principles.

10.4.1. Sponsor

TG Therapeutics, Inc. the Sponsor, will provide financial support, general oversight, and decision-making for the registry. The Sponsor may transfer any or all of its study-related responsibilities to a contract research organization and other third parties; however, the Sponsor retains overall accountability for these activities.

10.4.2. Principal Investigator

The principal investigator is responsible for providing oversight of the registry and all submissions (protocol, amendments) to the IRB. The principal investigator may delegate responsibilities for study-related tasks, where appropriate, to individuals sufficiently qualified by education, training, and experience, in accordance with applicable regulations. The principal investigator will be available to the Sponsor and the SAC for ongoing consultations regarding the review, analysis, and conduct of the registry.

10.4.3. Co investigators

No co-investigators are involved in this study.

10.4.4. Scientific Advisory Committee

The SAC is responsible for overseeing the scientific affairs of the registry, including its ongoing monitoring. The SAC is an independent (not associated with the Sponsor) group of recognized experts in the fields of teratology, epidemiology, maternal and fetal medicine, and therapeutic areas from academia and private practice. They will meet twice annually prior to finalization of each annual summary report, first to review and classify reported MCMs (as described in Section 9.3.3) prior to annual analyses, and again after the analyses are complete to review the accumulated body of data from the registry and to carry out any actions required, including review of recruitment and retention, and review and interpretation of analyses, reports, and publications of registry data. As warranted, the SAC may recommend specific strategies to heighten awareness of the registry. The SAC may meet on ad hoc occasions, if indicated, to address potential signals or other issues that arise during the course of the registry.

A critical function of the SAC is to detect potential signals or patterns, to evaluate them, and to determine the necessary course of action if a signal is generated. To aid in this function, the registry has adopted a plan used by other registries, which applies the “Rule of Three” for detecting a potential signal and the “threshold” strategy for determining the appropriate course of action (Covington 2004). The “Rule of Three” convention specifies that once 3 like MCMs have accumulated with any specific exposure, these cases are flagged for immediate review. For a specific defect that occurs at a rate of <1/700 in the general population, the likelihood of 3 defects occurring in a cohort of up to 600 live births by chance alone is <5%. To ensure prompt, responsible, and appropriate action in the event of a potential signal, the registry will employ the strategy of “threshold” based on the Council of International Organizations for the Medical Sciences (CIOMS 1999). The threshold for action will be determined by the extent of certainty about the cases and tempered by the specifics of the cases.

The responsibilities of the SAC will be described in a charter to which each SAC member will agree.

10.4.5. Virtual Research Coordination Center

The VRCC is responsible for assisting the principal investigator in all aspects of participant recruitment, informed consent, data collection, and management. As noted in Section 10, the VRCC staff are fully trained on and compliant with SOPs regarding the protection of human subjects and data privacy.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

The registry will limit active solicitation of AEs to specific maternal, fetal, and infant outcomes, including death (Section 8). All AEs/SAEs reported, regardless of solicitation, will be submitted to the Sponsor's pharmacovigilance department. SAEs will be submitted immediately and no greater than within 1 business day of awareness; AEs will be submitted no greater than within 2 business days of awareness. The Sponsor will report AE data, as applicable, to the appropriate regulatory authorities within the required timeframe, as required. Further details on how AEs are defined, handled, and reported will be included in the safety and medical management plan.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The registry will produce annual interim progress reports. A final comprehensive study report will be developed after the conclusion of the registry. These reports will be submitted to the appropriate regulatory authorities as well. Reports will include a presentation of the registry design, methodology, and results to date. The final, comprehensive study report will additionally include an interpretive discussion of the biostatistical analysis results.

13. REFERENCES

American Academy of Pediatrics (AAP). Recommendations for preventive pediatric health care.https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf. Updated March 2021. Accessed August 8, 2022.

American Academy of Pediatrics (AAP). Recommendations for preventive pediatric health care.https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf. Updated March 2021. Accessed August 8, 2022.

American College of Obstetricians and Gynecologists (ACOG). ACOG Obstetric Care Consensus No. 10: management of stillbirth. Obstet Gynecol. 2020;135(3):e110-32.

American College of Obstetricians and Gynecologists (ACOG). ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol. 2002;99(1):159-167.

American College of Obstetricians and Gynecologists (ACOG). Committee Opinion No 700: methods for estimating the due date. Obstet Gynecol. 2017;129(5):e150-4.

American Diabetes Association (ADA). Gestational diabetes mellitus. Diabetes Care. 2004;27 Suppl 1:S88-90.

Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ. 2013 Nov 7;347:f6564.

Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. J Pediatr. 1967;71(2):159-63.

Butwick AJ, Druzin ML, Shaw GM, Guo N. Evaluation of US State-Level Variation in Hypertensive Disorders of Pregnancy. JAMA Netw Open. 2020 Oct 1;3(10):e2018741.

Centers for Disease Control and Prevention (CDC), Division of Birth Defects and Developmental Disabilities. Birth defects toolkit. Appendix B: external minor congenital anomalies. Updated November, 2019. www.cdc.gov/ncbddd/birthdefects/surveillancemanual/appendices/appendix-b.html. Accessed August 8, 2022.

Centers for Disease Control and Prevention (CDC), Division of Birth Defects and Developmental Disabilities. Birth defects and genetic diseases branch 6-digit codes for reportable congenital anomalies. Updated 2021. www.cdc.gov/ncbddd/birthdefects/macdp.html. Accessed August 8, 2022.

Centers for Disease Control and Prevention (CDC). High blood pressure during pregnancy. 2020b. https://www.cdc.gov/bloodpressure/pregnancy.htm. Accessed February 21, 2022.

Centers for Disease Control and Prevention (CDC). Birth defects surveillance toolkit. 1.4 Congenital anomalies – definitions. Updated November, 2020a. www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-1/chapter1-4.html. Accessed August 8, 2022.

Centers for Disease Control and Prevention (CDC). CDC's developmental milestones. Updated 2022. www.cdc.gov/ncbddd/actearly/milestones/index.html. Accessed February 21, 2022.

Centers for Disease Control and Prevention (CDC). National Center for Health Statistics. WHO growth standards are recommended for use in the U.S. for infants and children 0 to 2 years of age. Updated September, 2010. www.cdc.gov/growthcharts/who_charts.htm. Accessed August 8, 2022.

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

Council for International Organizations of Medical Sciences (CIOMS) Working Groups III and V. Guidelines for preparing core clinical-safety information on drugs. 2nd ed. Geneva, Switzerland: World Health Organization, 1999.

Council for International Organizations of Medical Sciences (CIOMS). CIOMS Cumulative Pharmacovigilance Glossary Version 1.0. 2021; https://cioms.ch/wp-content/uploads/2021/03/CIOMS-Cumulative-PV-Glossary-v1.0.pdf. Accessed March 23, 2023.

Covington DL, Mates H, Churchill P, Golembesky A, McKain LF. Improving accuracy in enrollment targets for pregnancy registries. Pharmacoepidemiol Drug Saf. 2010;19(suppl 1):S71 2.

Covington DL, Tilson H, Elder J, et al. Assessing teratogenicity of antiretroviral drugs: monitoring and analysis plan of the Antiretroviral Pregnancy Registry. Pharmacoepidemiol Drug Saf. 2004;13:537-45.

Coyle PK, Sinclair SM, Scheuerle AE, Thorp JM Jr, Albano JD, Rametta MJ. Final results from the Betaseron (interferon β-1b) Pregnancy Registry: a prospective observational study of birth defects and pregnancy-related adverse events. BMJ Open. 2014;4:e004536.

Coyle PK. Management of women with multiple sclerosis through pregnancy and after childbirth. Ther Adv Neurol Disord. 2016;9(3):198-210.

Dahl J, Myhr KM, Daltveit AK, Hoff JM, Gilhus NE. Pregnancy, delivery, and birth outcome in women with multiple sclerosis. Neurology. 2005;65(12):1961-3.

Dobson R, Rog D, Ovadia C, et al. Anti-CD20 therapies in pregnancy and breast feeding: a review and ABN guidelines. Pract Neurol. 2023;23(1):6-14.

El-Masri MM, Fox-Wasylyshyn SM. Missing data: An introductory conceptual overview for the novice researcher. Can J Nurs Res. 2005;37(4):156-71.

European Medicines Agency, Committee for Medicinal Products for Human Use. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. EMA/CHMP/771815/2011 Rev. 2, 2015.

Feldkamp ML, Botto LD, Carey JC. Reflections on the etiology of structural birth defects: Established teratogens and risk factors. Birth Defects Res A Clin Mol Teratol. 2015;103(8):652 5.

Fong A, Chau CT, Quant C, et al. Multiple sclerosis in pregnancy: prevalence, sociodemographic factors, and obstetrical outcomes. J Matern Fetal Neonatal Med. 2018;31(3):382-7.

Food and Drug Administration (FDA). Postapproval pregnancy safety studies: guidance for industry. 2019. https://www.fda.gov/media/124746/download. Accessed February 21, 2022.

Friend S, Richman S, Bloomgren G, et al. Evaluation of pregnancy outcomes from the Tysabri (natalizumab) pregnancy exposure registry: a global, observational, follow-up study. BMC Neurology. 2016;16:150.

Geissbühler Y, Vile J, Koren G, et al. Evaluation of pregnancy outcomes in patients with multiple sclerosis after fingolimod exposure. Ther Adv Neurol Disord. 2018;11:1756286418804760.

Giovannoni G, Butzkeuven H, Dhib-Jalbut S, et al. Brain health:time matters in multiple sclerosis. Mult Scler Relat Disord. 2016;(9 suppl 1):S5-48.

Gliklich R, Dreyer N, Leavy M, eds. Registries for evaluating patient outcomes: a user's guide; 4th Edition. Rockville, Maryland: sites/default/files Agency for Healthcare Research and Quality (AHRQ); 2020. https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registries-evaluating-patient-outcomes-4th-edition.pdf. Accessed August 8, 2022.

Gregory EC, Valenzuela CP, Hoyert DL. Fetal Mortality: United States, 2019. Natl Vital Stat Rep. 2021;70(11):1-20.

Guidelines for Good Pharmacoepidemiology Practices (GPP). Updated June, 2015. www.pharmacoepi.org/resources/policies/guidelines-08027/. Accessed February 21, 2022.

Hellwig K, Rog D, McGuigan C, Houtchens MK, Bruen DR, Mokliatchouk O, Branco F, Peng X, Everage NJ. Interim Analysis of Pregnancy Outcomes After Exposure to Dimethyl Fumarate in a Prospective International Registry. Neurol Neuroimmunol Neuroinflamm. 2021 Nov 23;9(1):e1114.

Holmes LB, Westgate MN. Inclusion and exclusion criteria for malformations in newborn infants exposed to potential teratogens. Birth Defects Res A Clin Mol Teratol. 2011;91(9):807 12.

Honein MA, Paulozzi LJ, Cragan JD, Correa A. Evaluation of selected characteristics of pregnancy drug registries. Teratology. 1999;60(6):356-64.

Houtchens MK, Edwards NC, Schneider G, et al. Pregnancy rates and outcomes in women with and without MS in the United States. Neurology. 2018;91(17):e1559-69.

Jones RK, Witwer E, Jerman J. Abortion incidence and service availability in the United States, 2017. New York, NY: Guttmacher Institute; 2019. https://www.guttmacher.org/report/abortion-incidence-service-availability-us-2017.

Kelly VM, Nelson LM, Chakravarty EF. Obstetric outcomes in women with multiple sclerosis and epilepsy. Neurology. 2009;73(22):1831-6.

Kennedy DL, Uhl K, Kweder SL. Pregnancy exposure registries. Drug Saf. 2004;27(4):215-28.

Kieseier BC, Benamor M. Pregnancy outcomes following maternal and paternal exposure to teriflunomide during treatment for relapsing-remitting multiple sclerosis. Neurol Ther. 2014 Nov 20;3(2):133-8.

MacDonald SC, McElrath TF, Hernández-Díaz S. Pregnancy outcomes in women with multiple sclerosis. Am J Epidemiol. 2018;188(1):57-66.

Martin JA, Hamilton BE, Osterman MJK, Driscoll AK. Births: Final data for 2019. Natl Vital Stat Rep. 2021;70(2): 1-51.

Mason CA, Kirby RS, Sever LE, Langlois PH. Prevalence is the preferred measure of frequency of birth defects. Birth Defects Res A Clin Mol Teratol. 2005;73(10):690-2.

Osterman MJK, Hamilton BE, Martin JA, Driscoll AK, Valenzuela CP. Births: Final data for 2020. Natl Vital Stat Rep. 2022; 70(17): 1-50.

Polifka JE, Friedman JM. Medical genetics: 1. Clinical teratology in the age of genomics. CMAJ. 2002;167(3):265-73.

Robins JM, Rotnitzky A, Zhao LP. Estimation of regression coefficients when some regressors are not always observed. J Am Stat Assoc. 1994;89(427):846-66.

Robins JM, Rotnitzky A. Semiparametric efficiency in multivariate regression models with missing data. J Am Stat Assoc. 1995;90(429):122-9.

Rosenberg SA, Zhang D, Robinson CC. Prevalence of developmental delays and participation in early intervention services for young children. Pediatrics. 2008 Jun;121(6):e1503-9.

Sandberg-Wollheim M, Alteri E, Moraga MS, Kornmann G. Pregnancy outcomes in multiple sclerosis following subcutaneous interferon beta-1a therapy. Mult Scler J. 2011;17(4):423-30.

Scharfstein DO, Rotnitzky A, Robins JM. Adjusting for nonignorable drop-out using semiparametric nonresponse models. J Am Stat Assoc. 1999;94(448):1096 1120.

Tanasescu R, Ionete C, Chou I, et al. Advances in the treatment of relapsing-remitting multiple sclerosis. Biomed J. 2014;37(2):41-9.

TERIS: the Teratogen Information System. https://deohs.washington.edu/teris/ Updated 2021. Accessed August 8, 2022.

TG Therapeutics Inc. BRIUMVI™ (ublituximab-xiiy) injection, for intravenous use [Package Insert]. 2022. https://www.tgtherapeutics.com/label-prescribing-info/uspi-briumvi.pdf

The Multiple Sclerosis International Federation. Atlas of MS, 3rd Edition (September 2020) https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms/ Accessed June 28, 2022.

US Census Bureau (2022). Age and Sex data, 2021 American Community Survey. https://data.census.gov/table?q=S0101&tid=ACSST5Y2021.S0101. Accessed 27 April 2023.

Varytė G, Arlauskienė A, Ramašauskaitė D. Pregnancy and multiple sclerosis: an update. Curr Opin Obstet Gynecol. 2021;33(5):378-383.

Veley K, Covington DL, Buus R, Chan RL, Churchill P. Sample size calculations for pregnancy registries: improving accuracy. Pharmacoepidemiol Drug Saf. 2020;29(3):537-8.

Villar J, Giuliani F, Fenton TR, et al. INTERGROWTH 21st very preterm size at birth reference charts. Lancet. 2016;387(10021):844-5.

Villar J, Ismail LC, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014;384(9946):857-68.

Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: a population-based estimate using health claims data. Neurology. 2019;92:e1029-40.

Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis. 2015;74(12):2107-2116.

Wu P, Velez Edwards DR, Gorrindo P, Sundermann AC, Torstenson ES, et al. Association between first trimester antidepressant use and risk of spontaneous abortion. Pharmacotherapy. 2019; 39(9): 889-898.

Zomerdijk IM, Ruiter R, Houweling LMA, et al. Dispensing of potentially teratogenic drugs before conception and during pregnancy: a population-based study. BJOG. 2015;122(8):1119-29.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Adopted by the ENCePP Steering Group on 15/10/2018

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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Ublituximab Pregnancy Registry: A Prospective Study of Pregnancy and Infant Outcomes in Patients Treated with BRIUMVI™

EU PAS Register® number: Study will be registered in the HMA-EMA Catalogues before study initiation

Study reference number (if applicable):

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]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☒	☐	☐	6

[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 1: Milestones	Yes	No	N/A	Section Number
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	7 and 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
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, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.2
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	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	☒	☐	☐	
4.2.2 Age and sex	☒	☐	☐	
4.2.3 Country of origin	☒	☐	☐	9.2.2
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	
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)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.2

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?	☒	☐	☐	9.3.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.3
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.7.1
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7.1

Comments:

Section 8: Effect measure 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)	☒	☐	☐	9.7.2.6

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)	☒	☐	☐	9.6.2

Section 9: Data sources	Yes	No	N/A	Section Number
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.6.2
9.1.3 Covariates and other characteristics?	☐	☐	☐	
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)	☒	☐	☐	9.6.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.6.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.6.2
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), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Annex 3
9.3.3 Covariates and other characteristics?	☐	☐	☒	
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 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.2
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5.2
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.2.5
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.2.8

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.3
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2.5 - 9.7.2.8

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)	☒	☐	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	
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).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5.2

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3

Section 13: Ethical/data protection issues		Yes	No	N/A	Section Number
13.2	Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3	Have data protection requirements been described?	☒	☐	☐	10

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: _____

Date: dd/Month/year

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

MACDP Birth Defects Code List

https://www.cdc.gov/ncbddd/birthdefects/documents/bpa-codes-rev2021-508c.xlsx

CDC List of Minor Congenital Anomalies

https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/appendices/appendix-b.html

List of comparator and excluded products

This list will be continually updated to reflect changes in access and adoption of treatment for MS and knowledge on teratogenic effects and evolving knowledge of the teratogenicity of medications.

Table 8: Comparator Products

Product	Brand name	Half-life	Maximum 5 half lives
Alemtuzumab	Lemtrada	14 days	70 days
Azathioprine[a]	Azasan, Imuran	5 hours	1 day
Cladribine[a]	Mavenclad	1 day	5 days
Dimethyl fumarate	Tecfidera	1 hour	1 day
Diroximel fumarate	Vumerity	1 hour	1 day
Fingolimod	Gilenya, Tascenso ODT	6 to 9 days	45 days
Glatiramer acetate	Copaxone, Glatopa	NA	1 day
Interferon beta-1a	Avonex	19 hours (range: 8 to 54 hours)	4 days
Interferon beta-1a	Rebif	69 ± 37 hours	15 days
Interferon beta-1b	Betaseron, Extavia	8 minutes to 4.3 hours	1 day
Mitoxantrone[a]	Novantrone	75 hours (range: 23 to 215 hours)	16 days
Monomethyl fumarate	Bafiertam	0.5 hours	1 day
Natalizumab	Tysabri	11 ± 4 days	55 days
Ozanimod	Zeposia	21 hours; active metabolite 11 days	55 days
Peginterferon beta-1a	Plegridy	78 hours	17 days
Ponesimod	Ponvory	30 to 33.5 hours	7 days
Siponimod	Mayzent	30 hours	7 days

Product	Brand name	Half-life	Maximum 5 half lives
Teriflunomide	Aubagio	18 to 19 days	95 days

NA = not available
List excludes anti-CD20 monoclonal antibodies (ocrelizumab, ofatumumab).
[a] Indicates teratogen used to treat MS (azathioprine, cladribine, mitoxantrone); exposure to teratogens will be handled in the analysis as described in Section 9.6.5.3 and Section 9.7.2.7.

Table 9: Excluded Products

Product	Brand name	Half-life	Maximum 5 half lives
Ocrelizumab	Ocrevus	26 days	130 days
Ofatumumab	Kesimpta	16 days	80 days

List includes all anti-CD20 monoclonal antibodies other than BRIUMVI™.

List of Teratogens

Table 10 provides a list of teratogens. This list will be continually updated based on the data available in the TERIS database of teratogenic agents and recent publications (Feldkamp 2015; Polifka 2002; TERIS 2020; Zomerdijk 2015).

Table 10: Teratogens

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
Androgen	Methyltestosterone	6 to 8 h	2 days prior to DOC	1st, 2nd, and 3rd trimesters
	Testosterone (unmodified)	10 to 100 min	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Testosterone cypionate	8 d	40 days prior to DOC	1st, 2nd, and 3rd trimesters
	Testosterone enanthate	4.5 d	23 days prior to DOC	1st, 2nd, and 3rd trimesters
	Mesterolone	12 to 13 h	3 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Nandrolone	144 to 288 h	2 months prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Oxandrolone	13.3 h	3 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Prasterone	12 h	3 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Fluoxymesterone	9.2 h	2 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
Angiotensin II receptor antagonist	Azilsartan	11	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Candesartan	9 h	2 days prior to DOC	1st, 2nd, and 3rd trimesters
	Eprosartan	20 h	5 days prior to DOC	1st, 2nd, and 3rd trimesters
	Irbesartan	11 to 15 h	4 days prior to DOC	1st, 2nd, and 3rd trimesters
	Losartan	2 h	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Olmesartan	13 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Sparsentan	9.6 h	2 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Tasosartan	Not available, but half-life of ARBs range from 1 to 3 d	15 days prior to DOC	1st, 2nd, and 3rd trimesters
	Telmisartan	24 h	5 days prior to DOC	1st, 2nd, and 3rd trimesters
	Valsartan	6 h	2 days prior to DOC	1st, 2nd, and 3rd trimesters
	Benazepril	10 to 11 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
Angiotensin-converting enzyme inhibitors	Captopril	2 h	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Cilazapril	9 h	2 days prior to DOC	1st, 2nd, and 3rd trimesters
	Enalapril	11 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Fosinopril	11.5 to 14 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Lisinopril	12 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Moexipril	12 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Perindopril	0.8 to 1 h	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Quinapril	3 h	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Ramipril	13 to 17 h	4 days prior to DOC	1st, 2nd, and 3rd trimesters
	Trandolapril	6 h	2 days prior to DOC	1st, 2nd, and 3rd trimesters
Antiarrhythmic	Amiodarone	61 d	10 months prior to DOC	1st, 2nd, and 3rd trimesters
Antibiotic	Sulfamethoxazole/ trimethoprim	8 to 10 h	3 months prior to DOC	3 months prior to conception and 1st trimester for MCMs and 2nd trimester for preterm birth and LBW
Anticoagulant	Acenocoumarol	8 to 11 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Dicumarol	1 to 2 d	2 weeks prior to DOC	At least 2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Phenprocoumon (Fenprocoumon)	4 to 6 d	1 month prior to DOC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Warfarin	40 h	2 weeks prior to DOC	At least 2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
Anticonvulsant	Trimethadione/ paramethadione	Paramethadione: 12 to 24 h Trimethadione: 11 to 16 h	5 days prior to DOC	1st, 2nd, and 3rd trimesters
	Valproic acid/ valproate	9 to 16 h	4 days prior to DOC	Primarily 1st trimester, but MCMs have been associated with 2nd and 3rd trimester exposures.
	Carbamazepine	12 to 65 h	2 weeks prior to DOC	1st, 2nd, and 3rd trimesters
	Ethotoin	3 to 9 h	2 days prior to DOC	1st, 2nd, and 3rd trimesters
	Phenytoin/ fosphenytoin	Phenytoin: 7 to 42 h Fosphenytoin: 15 min	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Primidone	10 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Topiramate	21 h	5 days prior to DOC	1st, 2nd, and 3rd trimesters
	Ethosuximide	17 to 56 h	12 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Oxcarbazepine	Oxcarbazepine: immediate-release formulations, about 2 h; extended-release tablet, 7 to 11 h Active metabolite, 10–monohydroxy: 9 to 11 h	3 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Sultiame	24 h	5 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Vigabatrin	10.5 h	3 days prior to DOC	Unknown
	Phenobarbital	70 to 140 h	1 month prior to DOC	1st, 2nd, and 3rd trimesters
	Methylphenobarbital	34 h	8 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
Antidepressants	Paroxetine	21 h	5 days prior to DOC	1st trimester
Antifungal	Fluconazole[b]	30 h	2 weeks prior to DOC	2 weeks prior to conception and 1st trimester
	Flucytosine	2.4 to 4.8 h	1 day prior to DOC	1st trimester
Antineoplastic	Aminopterin	12 to 24 h	5 days prior to DOC	1st, 2nd, and 3rd trimesters
	Asparaginase	5.7 d	3 months prior to DOC	3 months prior to conception and 1st, 2nd, and 3rd trimesters
	Axitinib	2.5 to 6.1 h	1 week prior to DOC	1 week prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Brentuximab vedotin	4 to 6 d	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Methotrexate[c]	55 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Crizotinib	42 h	45 days prior to DOC	45 days prior to conception and 1st, 2nd, and 3rd trimesters
	Cytarabine	1 to 3 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Daunorubicin	The plasma half-life of daunorubicin averages 45 minutes in the initial phase and 18.5 hours in the terminal phase. By 1 hour after administration of daunorubicin, the predominant form of the drug in plasma is the metabolite daunorubicinol, which has as average terminal plasma half-life of 26.7 hours	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Exemestane	24 h	1 month prior to DOC	1 month prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Mechlorethamine	15 min	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Mercaptopurine[c]	10 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Vinblastine	24.8 h	6 days prior to DOC	1st, 2nd, and 3rd trimesters
	Cyclophosphamide	3 to 12 h	12 months prior to DOC	12 months prior to conception and 1st trimester
	Altretamine	4.7 to 10.2 h	3 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Amsacrine	8 to 9 h	3 months prior to DOC	3 months prior to conception and 1st, 2nd, and 3rd trimesters
	Bevacizumab	480 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Bleomycin	2 h	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Bortezomib	40 to 193 h	7 months prior to DOC	7 months prior to conception and 1st, 2nd, and 3rd trimesters
	Busulfan	2.3 to 3.4 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Capecitabine	0.75 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Carboplatin	2.6 to 5.9 h	5 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Carmustine	15 to 75 min	3 months prior to DOC	3 months prior to conception and 1st, 2nd, and 3rd trimesters
	Cetuximab	63 to 230 h	2 months prior to DOC	2 months prior to conception and 1st, 2nd, and 3rd trimesters
	Chlorambucil	1.5 h	1 day prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Cisplatin	20 to 30 min	14 months prior to DOC	14 months prior to conception and 1st, 2nd, and 3rd trimesters
	Cladribine	1 d	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Clofarabine	5.2 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Dacarbazine	5 h	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Dactinomycin	36 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Dasatinib	3 to 5 h	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Docetaxel	11.1 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Doxorubicin	20 to 48 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Epirubicin	31.1 h +/- 6 h to 35.3 h +/- 9 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Erlotinib	36.2 h	2 weeks prior to DOC	2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Estramustine	10 to 20 h	5 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Etoposide	4 to 11 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Fludarabine	20 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Fluorouracil	8 to 20 min	3 months prior to DOC	3 months prior to conception and 1st, 2nd, and 3rd trimesters
	Gemcitabine	1.7 to 19.4 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Hydroxycarbamide	2 to 4.5 h	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Idarubicin	20 to 22 h	6.5 months prior to DOC	6.5 months prior to conception and 1st, 2nd, and 3rd trimesters
	Ifosfamide	15 h	4 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Imatinib	18 h	2 weeks prior to DOC	2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Irinotecan	6 to 12 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Lapatinib	24 h	1 week prior to DOC	1 week prior to conception and 1st, 2nd, and 3rd trimesters
	Lomustine	16 to 48 h	2 weeks prior to DOC	2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Melphalan	10 to 75 min	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Mitocycine	46 min	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Mitoxantrone	23 to 215 h	45 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Nelarabine	Adults: prodrug: 30 min; Ara-G: 3 h	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Oxaliplatin	392 h	9 months prior to DOC	9 months prior to conception and 1st, 2nd, and 3rd trimesters
	Paclitaxel	13 to 52 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Pemetrexed	3.5 h	1 day prior to DOC	Unknown
	Pembrolizumab	22d	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Pentostatin	5.7 h	2 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Procarbazine	(IV), approximately 10 min	1 day prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Raltitrexed	260 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Sorafenib	25 to 48 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Streptozocin	Systemic: 35 min unchanged drug; 40 h metabolites	1 month prior to DOC	1 month prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Sunitinib	40 to 60 h	1 month prior to DOC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Tegafur	6.7 to 11.3 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Temozolomide	1.8 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Teniposide	5 h	1 day prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Thioguanine	80 min	1 day prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Thiotepa	1.4 to 3.7 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Topotecan	2 to 3 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Vincristine	85 h	6 months prior to DOC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Vindesine	2.9 h	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Vinorelbine	27.7 to 43.6 h	10 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Lenalidomide	3 h	4 weeks prior to DOC	4 weeks prior to conception and 1st, 2nd, and 3rd trimesters
Antithyroid	Propylthiouracil	1 to 2 h	1 day prior to DOC	1st and 2nd trimesters
	Methimazole	4.9 to 5.7 h	2 days prior to DOC	1st, 2nd, and 3rd trimesters
	Radioiodine	192 h	12 months prior to DOC	6 to 12 months prior to conception and 1st, 2nd, and 3rd trimesters
Antiviral	Ribavirin	12 d	2 months prior to DOC	1st, 2nd, and 3rd trimesters
Endothelin receptor antagonist	Ambrisentan	15 h	4 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Bosentan	5 to 8 h	2 days prior to DOC	2 days prior to conception and 1st trimester
	Macitentan	16 to 48 j	10 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
Estrogen	Diethylstilbestrol	Diethylstilbestrol reaches peak concentration within 20–40 min, having a primary half-life of 3 to 6 r. It has a terminal half-life of 2 to 3 d due to entero-hepatic circulation	15 days prior to DOC	1st, 2nd, and 3rd trimesters
Immunomodulatory agent	Mycophenolate mofetil	16 h	4 days prior to DOC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Thalidomide	5 to 7 h	1 month prior to DOC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Penicillamine	2 to 4 h	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Azathioprine[c]	5 h	1 day prior to DOC	Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy"
	Leflunomide	432 to 456 h	2 years prior to DOC	2 years prior to conception and 1st, 2nd, and 3rd trimesters
	Mycophenolic acid	8 to 16 h	4 days prior to DOC	Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy"
Mood stabilizer	Lithium	24 h	5 days prior to DOC	1st, 2nd, and 3rd trimesters
NSAID	Aspirin	2 to 30 h	7 days prior to DOC	2nd and 3rd trimesters; unlikely risk associated with 1st trimester exposure
	Ibuprofen	1.9 to 2.2 h	1 day prior to DOC	2nd and 3rd trimesters; unlikely risk associated with 1st trimester exposure

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Indomethacin	4.5 h	1 day prior to DOC	2nd and 3rd trimesters; unlikely risk associated with 1st trimester exposure
	Naproxen	12 to 17 h	4 days prior to DOC	2nd and 3rd trimesters; unlikely risk associated with 1st trimester exposure
Prostaglandins analog	Misoprostol	20 to 40 min	1 month prior to DOC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
Retinoid	Alitretinoin	9 h	1 month prior to DOC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Tretinoin	0.5 to 2 h	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Vitamin A	TERIS only notes "long half-life"; 75 days per google search	12 months prior to DOC	1st, 2nd, and 3rd trimesters; doses above 10,000 IU/day may be teratogenic
	Acitretin	acitretin: 33 to 96 h; cis-acitretin: 28 to 157 h	3 years prior to DOC	3 years prior to stopping treatment and throughout pregnancy, especially 1st trimester
	Etretinate	120 d	3 years prior to DOC	3 years prior to stopping treatment and throughout pregnancy, especially 1st trimester

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
	Isotretinoin	10 to 12 h	1 month prior to DOC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Tazarotene	18 h	4 days prior to DOC	1st, 2nd, and 3rd trimesters
	Retinol	2 to 9 h	12 months prior to DOC	12 months prior to conception and 1st trimester
Steroid	Danazol	9.7 to 23.7 h	5 days prior to DOC	1st, 2nd, and 3rd trimesters
Tetracycline antibiotic	Demeclocycline	10 to 17 h	4 days prior to DOC	2nd and 3rd trimesters
	Oxytetracycline	6 to 11 h	3 days prior to DOC	2nd and 3rd trimesters
	Tetracycline	6 to 11 h	3 days prior to DOC	2nd and 3rd trimesters; limited data for 1st trimester exposure
	Chlortetracycline	5.6 h	2 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Doxycycline	18 to 22 h	5 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Methacycline	14 to 22 h	5 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Minocycline	11 to 24.31 h	6 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Tigecycline	27 to 43 h	9 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[a]	Relevant Exposure Window
Other	Methylene blue	24 h	5 days prior to DOC	1st, 2nd, and 3rd trimesters
	Riociguat	12 h	3 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

d = day; h = hour; IV = intravenous; LBW = low birth weight; MCM = major congenital malformation; min = minute; NSAIDs = nonsteroidal anti inflammatory drugs; TERIS = Teratogen Information System; y = year.
[a] A woman will be considered exposed during the 1st trimester, if a dose is taken during this pre-conception exposure window. Based on 5*half-life or relevant exposure window, whichever is longer.
[b] Only applies to ≥2 doses during pregnancy.
[c] Teratogenic risk is low; however, exposure during pregnancy may be associated with other adverse outcomes, including preterm birth and intrauterine growth restriction.
Sources: Eltonsy et al. (2016); TERIS (2021); DrugBank online available at https://go.drugbank.com; product labels, which are available at: https://www.accessdata.fda.gov/scripts/cder/daf/ and https://dailymed.nlm.nih.gov/dailymed/index.cfm summary of product characteristics at https://www.ema.europa.eu/en/medicines and https://products.mhra.gov.uk/, product monographs at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.

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I approve this document
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