PASS Information

Title	A Post-Authorization Study to Characterize the Safety of BRIUMVI (ublituximab) Use in Pregnant Patients with Multiple Sclerosis Using Data from a US Administrative Healthcare Claims Database
Protocol version identifier	Version 1.0 (EMA-only)
Date of last version of protocol	21 Mar 2024
EU PAS register number	Study will be registered in the HMA-EMA Catalogues before study initiation
Active substance	Ublituximab (L04AG14)
Medicinal product	BRIUMVI
Product reference	EMEA/H/C/005914
Procedure number	Not applicable
Marketing authorisation holder(s)	Neuraxpharm Pharmaceuticals, S.L.
Joint PASS	No
Research question and objectives	The objective of this retrospective cohort study is to assess pregnancy and infant outcomes among pregnant individuals with multiple sclerosis (MS) who were exposed to BRIUMVI during pregnancy, compared to two unexposed patient groups: (a) Disease-matched pregnant individuals exposed to other MS therapies and (b) Disease-matched pregnant individuals who were not exposed to any treatment for MS at the time of the estimated start of pregnancy (estimated date of conception (EDC)) or at any time during pregnancy. Specifically, the primary study objective is: • To assess the frequency of major congenital malformations (MCMs) among infants of subjects with MS exposed to BRIUMVI during pregnancy and to compare the rates to two reference groups: – Infants of subjects with MS exposed prenatally to non-BRIUMVI disease- modifying therapies for the treatment of MS – Infants of subjects with MS not exposed prenatally to any treatment for MS. Secondary study objectives are:

	• To assess the frequency of preterm births and small for gestational age among infants of subjects with MS exposed to BRIUMVI during pregnancy. • To assess rates of pregnancy complications (eclampsia, pre-eclampsia, placental abruption, gestational diabetes) and outcomes (spontaneous abortions, stillbirths) among subjects with MS exposed to BRIUMVI during pregnancy. • To compare the rates of pregnancy complications, outcomes, and infant outcomes between subjects with MS exposed to BRIUMVI during pregnancy and two reference groups: – Subjects with MS exposed prenatally to non-BRIUMVI disease- modifying therapies for the treatment of MS – Subjects with MS not exposed prenatally to any treatment for MS.
Country(-ies) of study	United States of America
Author	Diego Wyszynski, MD, MHS, PhD

Marketing authorisation holder(s)

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2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
ADCC	Antibody-dependent cellular cytotoxicity
BHI	Blue Health Initiative
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIS	Clinically isolated syndrome
CNS	Central nervous system
CPT	Current Procedural Terminology
DMT	Disease-modifying therapy
EDC	Estimated date of conception
EHR	Electronic health record
FDA	Food and Drug Administration
Fc	Fragment crystallizable
FL	Follicular lymphoma
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IFN	Interferon
Ig	Immunoglobulin
IPTW	Inverse probability of treatment weighting
IV	Intravenous
LMP	Last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major congenital malformation
MS	Multiple sclerosis
NDC	National Drug Code
NK	Natural killer
PPV	Positive predictive value
PS	Propensity score
RRMS	Relapsing-remitting multiple sclerosis
SAB	Spontaneous abortion

Abbreviation or Term	Definition
SAP	Statistical Analysis Plan
SD	Standard deviation
SGA	Small for gestational age
SOC	System organ class
SPMS	Secondary progressive multiple sclerosis

3. RESPONSIBLE PARTIES

Name, Degree(s)	Title/Role	Affiliation
Diego Wyszynski, MD, MHS, PhD	Principal Investigator	CorEvitas, part of Thermo Fisher Scientific
Yanzhi Hsu, PhD	Vice President, Biostatistics	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 Retrospective Study of Pregnancy and Infant Outcomes in Patients Treated with BRIUMVI™
Study Number:	TG1101-RMS404
Study Phase:	Post-marketing Retrospective Pregnancy Registry
Location:	United States
Primary Objective:	To assess the frequency of major congenital malformations (MCMs) among infants of subjects with MS exposed to BRIUMVI during pregnancy, and to compare to two reference groups: 1. infants of subjects with MS exposed to non-BRIUMVI disease-modifying therapies for the treatment of MS during pregnancy, and 2. infants of subjects with MS not exposed to any treatment for MS during pregnancy.

Methodology:

The study will involve a retrospective analysis of pregnant subjects diagnosed with MS who were exposed to BRIUMVI at the time of the EDC or at any time during pregnancy. The subjects' de-identified data will be obtained from a prospectively collected administrative claims dataset sourced from commercial health plans in the United States. Further details on how adverse events are defined, handled, and reported will be included in the relevant adverse event reporting plan (AERP).

The retrospective analysis will include three cohorts for comparison:

- Cohort 1 – BRIUMVI-Exposed Cohort: This group will include subjects with MS who were exposed to BRIUMVI at the time of the EDC or at any time during pregnancy. This cohort will be compared to the unexposed cohorts.
- Cohort 2 – BRIUMVI-Unexposed, Disease-Modifying Therapy (DMT)-Exposed Comparison Cohort: This group will comprise subjects with MS who were exposed to DMTs approved for the treatment of MS other than BRIUMVI at the time of the EDC or at any time during pregnancy.
- Cohort 3 – Untreated Comparison Cohort: This group will consist of subjects with MS who were not exposed to any treatment for MS at the time of the EDC or at any time during pregnancy.

Eligible subjects for the exposed cohort and two comparison groups will be identified from the administrative claims data, using the following criteria:

Subjects must be female, between the ages of 15 and 50, and pregnant during the study period. Pregnancies will be identified through claims data, and validated algorithms will be employed to estimate the first day of the last menstrual period (LMP) and the EDC. Additionally, the end of the pregnancy will be determined through this process.

Number of Participants (planned):

The retrospective study aims to include as many eligible BRIUMVI-exposed pregnancies as possible, based on the available claims data. However, the sample size will be constrained by the number of eligible pregnancies observed in the data source.

The target sample size was calculated to adequately power the comparisons between the exposed and comparator cohorts for the primary outcome, major congenital malformations (MCMs) among live births. Assuming a baseline rate of 3%, which aligns with the Center for Disease Control and Prevention (CDC) reported prevalence at birth of birth defects in the United States, detecting a relative risk of 2.5 with 80% power would necessitate 304 live births in the BRIUMVI-exposed cohort, and 608 live births in each of the comparison cohorts (assuming a 1:2 ratio of eligible exposed to controls subjects). To account for non- live births (assuming 67% of pregnancies result in a live birth) and the percentage of pregnancies linkable to infants within the claims data (84% of live births are linkable between mother and infant), the study will need to identify 540 pregnancies eligible for the BRIUMVI-exposed cohort and 1,080 pregnancies eligible for each comparison cohort. Accounting for continuous enrollment patterns in the data (assuming 64% are continuously enrolled), roughly 844 pregnancies will need to be initially identified for the BRIUMVI-exposed cohort (and 1,688 pregnancies in each comparison cohort) to enable observation throughout the pregnancy and for 6-month prior to the pregnancy.

Study Population:

Female, between the ages of 15 and 50, and pregnant during the study period.

Duration of Participation:

The study period will commence with the first observed claim for the administration of BRIUMVI within the data source. Data will be scanned for claims after BRIUMVI approval in the US (28 December 2022). A permanent insurance reimbursement code (HCPCS code J2329) was assigned to BRIUMVI, effective 1 July 2023. Therefore, it is anticipated that the earliest subject observed to have received BRIUMVI and eligible for inclusion in the analysis will be in July 2023 or later.

The study accrual period is expected to run through the year 2034.

The study period will begin 12 months before the initial observed claim for BRIUMVI administration within the claims data. This duration allows for the collection of data concerning pregnancies that may have commenced before a claim for BRIUMVI was made.

Pregnancies eligible for the comparison cohorts will be selected from the same time period as the BRIUMVI-exposed pregnancies.

Statistical Methods:

The detailed methodologies for summarizing and analyzing the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be dated, filed, and maintained by the sponsor. It is important to note that the SAP may modify the plans outlined in the protocol. Any major modifications related to the definitions for the outcomes or their analyses will be reflected in a protocol amendment.

Data analyses will be performed using Stata, R/RStudio, and/or SAS.

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	Upon marketing authorization in data sources December 28, 2022
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™ (ublituximab) is a novel, type I chimeric immunoglobulin (Ig)G1 monoclonal antibody that selectively binds to the trans-membrane CD20 antigen found on CD20 expressing B-lymphocytes. 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 (1). 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 (2). The clinical signs and symptoms in 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 (3).

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 (4).

7.3. Current Standard of Care

Control of relapses and reduction of inflammatory burden is the primary focus of therapy, as there is currently no cure. Therapies for MS 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 (5).

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) (6). 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.

7.4. Multiple Sclerosis Treatments and Adverse Pregnancy Outcomes

An analysis of postmarketing 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 (7, 8). 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 (9).

In contrast, none of the oral medications are currently recommended for use during pregnancy. These recommendations stem from a combination of adverse events observed in animal studies and a lack of adequate human data to confidently evaluate the risk. Teriflunomide, fingolimod, and dimethyl fumarate have shown potential for teratogenicity, embryo lethality, and growth retardation in multiple animal studies (9). However, analyses of exposure to fingolimod shortly before or during pregnancy in humans found that the prevalence of major malformations among live births was not significantly higher than in the general population, and no specific pattern of birth defects was identified (10).

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 (11). 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 (9, 12).

7.5. 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 (13). 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 (2, 10, 14). 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 (15). 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.

7.6. Potential Risks Associated with Pregnancy Exposure to BRIUMVI

7.6.1. 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 (16).

Weekly intravenous administration of BRIUMVI (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.

BRIUMVI-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, elongate 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 (16).

7.6.2. 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 (16).

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 (16).

7.7. 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 retrospective cohort study is to provide information on pregnancy 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 this retrospective cohort study is to assess pregnancy and infant outcomes among pregnant individuals with MS who were exposed to BRIUMVI during pregnancy, compared to two unexposed patient groups: (a) Disease-matched pregnant individuals exposed to other MS therapies and

(b) Disease-matched pregnant individuals who were not exposed to any treatment for MS at the time of the estimated start of pregnancy (estimated date of conception (EDC)) or at any time during pregnancy.

Specifically, the primary study objective is to assess the frequency of major congenital malformations (MCMs) among infants of subjects with MS exposed to BRIUMVI during pregnancy, and to compare to two reference groups: 1. infants of subjects with MS exposed to non-BRIUMVI disease-modifying therapies for the treatment of MS during pregnancy, and 2. infants of subjects with MS not exposed to any treatment for MS during pregnancy.

Secondary study objectives are:

- To assess rates of pregnancy complications (eclampsia, pre-eclampsia, placental abruption, gestational diabetes) and outcomes (spontaneous abortions, stillbirths) among pregnancies for subjects with MS, who were exposed to BRIUMVI during pregnancy.
- To assess the frequency of preterm births, and small for gestational age among infants of subjects with MS exposed to BRIUMVI during pregnancy.
- To compare the rates of pregnancy complications, outcomes, and infant outcomes between pregnancies for subjects with MS who were exposed to BRIUMVI during pregnancy and two reference groups:
  - Pregnancies for subjects with MS, who were exposed to non-BRIUMVI disease-modifying therapies for the treatment of MS during pregnancy.
  - Pregnancies for subjects with MS, who were not exposed to any treatment for MS during pregnancy.

  The analyses of infant outcomes will be conducted on the subset of live births, from among the eligible pregnancies.

The assessments will be based on secondary claims data.

The study aims to fulfill one of the post-marketing requirements (PMR 4337-4) set by the US FDA for the approval of BRIUMVI in the US. The study will be conducted in accordance with the May 2019 FDA Draft Guidance for Industry on Post-Approval Pregnancy Safety Studies (17). Furthermore, this study is included as an additional pharmacovigilance activity in the EU Risk Management Plan for BRIUMVI to characterize risks of BRIUMVI use associated with pregnancy.

9. RESEARCH METHODS

9.1. Study design

The study will involve a retrospective analysis of pregnant subjects diagnosed with MS who were exposed to BRIUMVI at the time of the EDC or at any time during pregnancy. The subjects' de-identified data will be obtained from a prospectively collected administrative claims dataset sourced from commercial health plans in the United States. Further details on how adverse events are defined, handled, and reported will be included in the relevant adverse event reporting plan (AERP).

The retrospective analysis will include three cohorts for comparison:

- Cohort 1 – BRIUMVI-Exposed Cohort: This group will include subjects with MS who were exposed to BRIUMVI at the time of the EDC or at any time during pregnancy. This cohort will be compared to the unexposed cohorts.
- Cohort 2 – BRIUMVI-Unexposed, Disease-Modifying Therapy (DMT)-Exposed Comparison Cohort: This group will comprise subjects with MS who were exposed to DMTs approved for the treatment of MS other than BRIUMVI at the time of the EDC or at any time during pregnancy.
- Cohort 3 – Untreated Comparison Cohort: This group will consist of subjects with MS who were not exposed to any treatment for MS at the time of the EDC or at any time during pregnancy.

9.2. Setting

9.2.1. Eligibility Criteria

Eligible subjects for the exposed cohort and two comparison groups will be identified from the administrative claims data, using the following criteria:

Subjects must be female, between the ages of 15 and 50, and pregnant during the study period. Pregnancies will be identified through claims data, and validated algorithms will be employed to estimate the first day of the last menstrual period (LMP) and the EDC. Additionally, the end of the pregnancy will be determined through this process (18).

The LMP will be estimated based on diagnosis and procedure codes that record the trimester or gestational age as of the date of service. For example, ICD-10-CM code Z3A.xx captures the weeks of gestation. In the absence of codes that inform the trimester or gestational age, the algorithm will use an established number of days prior to the end of pregnancy, depending on the type of pregnancy outcome.

The EDC will be computed as date of LMP plus 14 days. The EDC will be used as the index date for each pregnancy.

The end of the pregnancy will be defined by ICD-10-CM diagnosis codes and/or Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) procedure codes that identify one of the following events (Annex 3):

- Live births

- Ectopic pregnancies
- Stillbirths
- Spontaneous abortions
- Elective abortions

Subjects with more than one pregnancy during the study period will be evaluated for each of the pregnancies. Each pregnancy may be eligible for inclusion in any of the cohorts, depending on the subject's drug exposure at the time of each pregnancy.

Subjects must have a documented diagnosis of MS. Confirmation of an MS diagnosis will require three or more occurrences of either (a) an MS diagnosis code on an inpatient or outpatient claim (ICD-10-CM code of G35) or (b) a claim for treatment with a DMT during the 6-months (180 days) prior to the EDC or during the first trimester (98 days) of the pregnancy. Multiple claims or multiple visits on the same day will be considered as one encounter. Prescriptions will be considered as separate encounters from inpatient and outpatient claims. At least one of the three or more encounters must be an inpatient or outpatient claim with a diagnosis code for MS (ICD-10-CM = G35). The presence of only one ICD-10-CM code for MS is not sufficient because it may include rule-out diagnoses. Subjects considered for Cohort 3 (subjects untreated for MS) will not have presence of DMT treatment (by definition), so confirmation of an MS diagnosis will require a minimum of 2 inpatient, or 3 outpatient claims with an ICD-10-CM diagnosis code of G35. This algorithm was shown to perform almost as well in validation studies as the requirement that includes DMT treatment and is the recommended algorithm when pharmacy data are not available (19).

The validated algorithm to identify an MS diagnosis is based on a one-year observation period. Application to eligible pregnant subjects in this study will include the 6 months prior to the EDC and the 3-month first trimester (Figure 1). Inclusion of the first trimester aims to capture diagnoses recorded during the subject's initial prenatal care visits, which may be infrequently captured on routine office visits or for subjects who have infrequent visits prior to the pregnancy.

Subjects must be continuously enrolled in the sourced health plan for the duration of the estimated pregnancy period, plus a 6-month baseline period prior to the EDC. The subject must be enrolled in a plan that provides medical and pharmacy coverage during this period so that all diagnoses, procedures, and treatments are captured in the claims and available for use in identifying comorbidities, treatment exposures, and outcomes.

Exposure to MS therapies at the time of or during the estimated pregnancy period will be used to assign pregnancies to one of the three possible cohorts. Methods to identify exposure are defined in the section below:

- Pregnancies for subjects with MS who have been exposed to BRIUMVI
- Pregnancies for subjects with MS who have been exposed to DMTs approved for the treatment of MS other than BRIUMVI
- Pregnancies for subjects with MS who were not exposed to DMTs approved for the treatment of MS at the time of the estimated EDC or during the pregnancy period

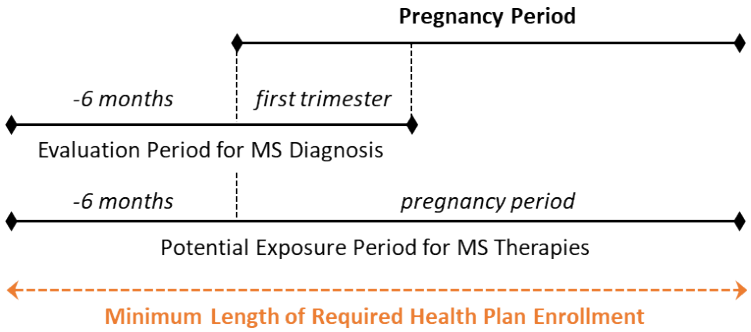
Subjects who have been exposed to any of the following classes of medications either at the time of the estimated EDC or during the pregnancy period will be excluded from all cohorts:

- Rituximab
- Products in the same class as BRIUMVI (CD20-directed cytolytic antibodies): ocrelizumab and ofatumumab
- Medications contraindicated in pregnancy
- Teratogenic and fetotoxic medications

Exposure during pregnancy will be determined from the date of administration (or days supply of a prescription) plus 5-times the product's half-life before the EDC (as defined in the Exposure section below). Medications used as exclusion criteria will be identified either through prescription claims (using National Drug Codes (NDCs)) or through HCPCS procedure codes (J-codes). These products for exclusion, along with the products' half-life and relative exposure period, are listed in Annex 3.

Pregnancies that have a recorded claim indicating an ectopic pregnancy or elective termination will be excluded from the study.

Figure 1: Eligibility requirements for confirmation of diagnosis and continuous enrollment



9.2.2. Study Period

The study period will commence with the first observed claim for the administration of BRIUMVI within the data source. Data will be scanned for claims after BRIUMVI approval in the US (28 December 2022). A permanent insurance reimbursement code (HCPCS code J2329) was assigned to BRIUMVI, effective 1 July 2023. Therefore, it is anticipated that the earliest subject observed to have received BRIUMVI and eligible for inclusion in the analysis will be in July 2023 or later.

The study accrual period is expected to run through the year 2034.

The study period will begin 12 months before the initial observed claim for BRIUMVI administration within the claims data. This duration allows for the collection of data concerning pregnancies that may have commenced before a claim for BRIUMVI was made.

Pregnancies eligible for the comparison cohorts will be selected from the same time period as the BRIUMVI-exposed pregnancies.

9.2.3. Follow-up

Each maternal subject will be observed during the estimated pregnancy period until the end of the pregnancy, such as the pregnancy termination date or the date of birth. Outcomes will be observed following the earliest date of drug exposure for the exposed cohorts, or at any time following EDC. Infants will be observed for up to one year (365 days) following the date of birth, but they will not be required to remain continuously enrolled in the health plan for the full 12 months. The observation period will conclude with either the date of an outcome of interest, disenrollment from the health plan, or end of the study period.

The periods used to identify each outcome are defined in Table 1.

Table 1: Observation periods for each outcome

Outcomes	Timing of Outcome
Pregnancy complications	During or after week 20 of pregnancy through end of pregnancy
Spontaneous abortion	Before week 20 of pregnancy
Stillbirth	At or after week 20 of pregnancy
Preterm birth	At birth
Major congenital malformations	At birth or up to 12 months of age
Small for gestational age	At birth

9.3. Variables

9.3.1. Exposure

The BRIUMVI-exposed cohort will include eligible pregnancies for which a procedure code for the administration of BRIUMVI (J2329) is recorded on a claim within 182 days (6 months) prior to the EDC or at any time during the pregnancy. The use of a 6-month period prior to pregnancy is based on the recommended use of contraception in the US Prescribing Information (USPI), "Females of reproductive potential should use effective contraception while receiving BRIUMVI and for 6 months after the last dose of BRIUMVI."

Exposure to other MS DMT treatments will be based on 5-times the half-life of each molecule (Table 2). The list of DMT treatments approved for MS will be reviewed and updated annually to include newly approved products as they become available during the course of the study.

Subjects will be considered exposed if the pattern of claims indicates usage of the drug as of EDC, or during, pregnancy.

- Subjects who received a drug through administration (as recorded by a claim with a HCPCS J-code) will be considered exposed at EDC if the most recent date of service prior to the estimated EDC falls within 5-times the half-life of the product (as defined in Table 2).
- Subjects who filled a prescription for one of the DMT treatments in the 6 months prior to the estimated EDC will be considered exposed at EDC if the days supply on

the recorded prescription, following dispensed date, plus 5-times the product's half-life (as defined in Table 2) extends up to or beyond the EDC.

Additionally, administration dates or prescription dispensed dates that fall during the pregnancy will qualify the subject as exposed to a DMT.

To evaluate spontaneous abortions, pregnancies will be considered exposed to a medication only if it is determined that the exposure occurred at EDC or before week 20 of pregnancy. To evaluate MCMs, infants will be considered exposed to a medication only if it was determined that the pregnancy was exposed at the EDC or during the first trimester.

Pregnancies that were exposed to both BRIUMVI and at least one of the eligible DMT treatments during the exposure period will be excluded from consideration in both of the exposed cohorts (Cohort 1 and 2).

Pregnancies for which there are no claims records for both BRIUMVI and any of the eligible DMT treatments throughout the pregnancy and have no claims that would indicate exposure as of the EDC, will be classified as unexposed. These pregnancies will be eligible for inclusion in the unexposed control group (Cohort 3).

Table 2: DMTs for the treatment of MS with dosing schedules (per USPI) to define exposure at time of pregnancy for Cohort 2

Product	Brand Name	Route of Administration	NDC (Product Code)	HCPS	Half-life	Exposure window prior to EDC
Alemtuzumab	Lemtrada	Infusion – at least 12 months after the last dose	58468-0200	J0202	2 weeks	70 days
Natalizumab	Tysabri	Infusion – every 4 weeks	64406-008	J2323	11 days	55 days
Glatiramer acetate	Copaxone	Injectable – once a day or 3 times per week	68546-325 68546-317 68546-325	J1595	unknown	1 day
Glatiramer acetate	Glatiramer Acetate Injection	Injectable – once a day or 3 times per week	0378-6960 0378-6961	J1595	unknown	1 day
Glatiramer acetate	Glatopa	Injectable – once a day or 3 times per week	0781-3250 0781-3234 63629-8815 63629-8816	J1595	unknown	1 day

Product	**Brand Name**	**Route of Administration**	**NDC (Product Code)**	**HCPS**	**Half-life**	**Exposure window prior to EDC**
Interferon beta-1a	Avonex	Injectable - once a week	59627-333 59627-222 59627-002 59627-003	J1826	19 hours	4 days
Interferon beta-1a	Rebif	Injectable – 3 times per week	44087-0022 44087-8822 44087-0044 44087-3344 44087-0188 44087-3322	J1826	69 hours	15 days
Interferon beta-1b	Betaseron	Injectable – every other day	50419-524	J1830	8 min - 4.3 hours	1 day
Interferon beta-1b	Extavia	Injectable – every other day	0078-0569	J1830	8 min - 4.3 minutes	1 day
Peginterferon beta- 1a	Plegridy	Injectable – once every 14 days	64406-011 64406-012 64406-015 64406-016 64406-017	N/A	78 hours	17 days
Dimethyl fumarate	Dimethyl Fumarate	Oral – twice a day	0093-9219 0093-9218 0378-0396 0378-0399 16729-416 16729-417 16729-418 24979-127 24979-128 31722-657 31722-658 31722-680 43547-024 43547-025 43598-429 43598-430	N/A	1 hour	1 day

Product	Brand Name	Route of Administration	NDC (Product Code)	HCPS	Half-life	Exposure window prior to EDC
			50090-5288 50090-6722 51407-441 51407-442 59651-083 59651-084 67877-555 67877-556 67877-557 68180-776 68180-777 68180-778 68462-307 68462-308 68462-570 69097-322 69097-323 69097-552 69238-1318 69238-1319 69238-1626 69539-042 69539-043 69539-240 70512-852 70512-853 70710-1204 70710-1205 70710-1416 70771-1530 70771-1531 70771-1532			
Dimethyl fumarate	Tecfidera	Oral – twice a day	64406-006 64406-005 64406-007	N/A	1 hour	1 day
Diroximel fumarate	Vumerity	Oral – twice a day	64406-020	N/A	1 hour	1 day

Product	Brand Name	Route of Administration	NDC (Product Code)	HCPS	Half-life	Exposure window prior to EDC
Fingolimod	Tascenso ODT	Oral – once daily	70709-062 70709-065	N/A	6 days	30 days
Fingolimod	Gilenya	Oral – once daily	0078-0607 0078-0965	N/A	6 days	30 days
Monomethyl fumarate	Bafiertam	Oral – twice a day	69387-001-01	N/A	0.5 hours	1 day
Ozanimod	Zeposia	Oral – once daily	59572-810 59572-820 59572-890	N/A	21 hours	5 days
Ponesimod	Ponvory	Oral – once daily	50458-702 50458-703 50458-704 50458-705 50458-706 50458-707 50458-708 50458-709 50458-710 50458-711 50458-720	N/A	33 hours	7 days
Siponimod	Mayzent	Oral – once daily	0078-0979 0078-0986 0078-1014	N/A	30 hours	7 days

Sourced from products' Prescribing Information documents and https://www.nationalmssociety.org/Treating-MS/Medications

9.3.2. Outcomes

Maternal, pregnancy, and infant outcomes will be identified in the claims data by examining the presence of diagnosis and/or procedure codes recorded on inpatient or outpatient claims. The linkage of mother and infant IDs will enable identification of outcomes for infants associated with the mother's exposure cohort. Infant's diagnoses may be captured in the mother's health plan claims data shortly after birth, if there is a delay in the enrollment of the infant in the health plan. Infant outcomes may be recorded on claims under the infant's member ID or on claims under the mother's member ID within the first 30 days following date of birth.Pregnancy complications and outcomes will be evaluated in all eligible pregnancies. Infant outcomes will be evaluated in the subset of live births, for which the mother can be linked to an infant.For each outcome, the first instance of a claim with the required code(s) must be recorded after the date of drug exposure.Where possible, published and validated algorithms will be used to confirm each

outcome. Algorithms published by the U.S. Food and Drug Administration (FDA) Sentinel Initiative will be leveraged as they become publicly available. Throughout the duration of the study, algorithms will be continually reviewed and refined to account for any modifications or newly published algorithms. Currently available algorithms, as well as ICD-10 codes and associated positive predictive values (PPVs) referenced in pregnancy publications, are documented in Annex 3. In addition to specifying diagnosis and procedure codes for identifying each outcome, algorithms may also require multiple occurrences, locations, and timing of codes recorded on claims. The final algorithms are subject to change as additional publications and validated algorithms become available. Any modifications to the algorithms will be documented in protocol amendments and shared with the FDA.

If an imbalance is detected for any outcome, CorEvitas will work with our data partner to conduct a medical chart review using validated outcomes. Our data source (BHI) is currently developing a plan to support validation of outcomes. The plan is not finalized yet, but it is assumed that it will involve chart retrieval and clinical review of charts. They expect to have the process approved in Q1 of 2024.Study outcomes will include the following pregnancy complications and outcomes, and infant outcomes.

Primary Outcome:

- Major congenital malformations (MCMs)

  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. Major structural birth defects will include ICD-10-CM codes for specific organ systems, as defined in validated claims algorithms (20). Minor congenital malformations will be excluded from consideration. MCMs will be reported in aggregate, and for each system organ class, as sample size permits.

Secondary Outcomes:

Maternal and Pregnancy Outcomes:

- Pregnancy complications

  Pregnancy complications, to the extent identifiable in claims, include eclampsia, pre-eclampsia, placental abruption, and gestational diabetes. Pregnancy complications will be reported in aggregate, and for each individual complication, as sample size permits.Spontaneous abortion

  An involuntary fetal loss or the expulsion of the products of conception occurring before 20 weeks of gestation. Only clinical spontaneous abortions recorded on medical claims with relevant diagnosis or procedure codes will be considered. Only participants who are exposed to BRIUMVI or a DMT before 20 weeks of gestation will be considered for the assessment of risk of miscarriage.Stillbirth

  Fetal loss occurring at or after 20 weeks of gestation, as recorded on claims with relevant ICD- 10-CM codes. Diagnosis codes indicating at least one stillbirth among multiple pregnancies (e.g., twins or other multiples) will be recorded as a stillbirth outcome.

Infant Outcomes:

- Preterm birth

  A live birth occurring at <37 gestational weeks. Preterm births will include those recorded with a relevant ICD-10-CD diagnosis code.

- Small for gestational age (SGA)

  Infant below the 10th percentile of birth weight for sex and gestational age. An SGA baby may be preterm or full-term. As birth weight is not recorded in administrative claims data, SGA will rely on the coding of relevant ICD-10-CM diagnosis codes.

9.3.3. Covariates

Using medical and pharmacy claims, data will be collected for the 6 months (180 days) prior to the EDC and during the first trimester of pregnancy (98 days) to construct baseline and existing patient demographics and clinical characteristics. These covariates will be used to ensure balance in the baseline characteristics of the exposed and comparison cohorts, and they will be included in the propensity score and regression models.

Including the first trimester in the assessment of comorbidities aims to capture chronic conditions that may be documented during the subject's initial prenatal care visits. This is important to account for conditions that might be infrequently recorded during routine office visits or for subjects with infrequent visits prior to the pregnancy.

The following covariates will be collected for each subject:

- Maternal age at conception
- Calendar year of conception
- US Census region
- Duration of MS
- MS relapses (during 6 months prior to pregnancy, as identified by a claims-based algorithm)
- DMT treatments used during the 6-months prior to pregnancy
- Drugs to treat MS symptoms (e.g., amantadine, baclofen)
- Charlson comorbidity index or other published comorbidity indices based on ICD-10-CM codes recorded on claims for the subject
- Specific comorbidities
  - Diabetes
  - Hypertension
  - Heart disease
  - Thyroid disease
  - Respiratory disease

  - Liver disease
  - Kidney disease
  - Malignancies
  - Anxiety/depression
- Obesity at conception (e.g., ICD-10-CM code O99.21x “Obesity complicating pregnancy, childbirth, and the puerperium”)
- Maternal weight gain during pregnancy (e.g., ICD-10-CM code O26.0x “Excessive weight gain in pregnancy”)
- Gestational age at drug exposure
- Tobacco use
- Alcohol use
- Substance use disorders
- Poor obstetric history (e.g., ICD-10-CM code O09.2x "Supervision of pregnancy with other poor reproductive or obstetric history”)
- Recurrent pregnancy loss (e.g., ICD-10-CM codes N96 “Recurrent pregnancy loss”, O26.2x “Pregnancy care for patient with recurrent pregnancy loss”)
- Health care resource utilization
  - Number of medications
  - Number of outpatient encounters
  - Number of inpatient stays

9.4. Data sources

The study will utilize a closed claims payer database licensed by CorEvitas from the Blue Health Initiative (BHI), which consists of individuals enrolled in commercial insurance plans in the United States. The database encompasses approximately 75 million individuals over the past three years, with 48 million having coverage for medical and pharmacy benefits. This extensive data repository includes medical and prescription claims, membership data, and provider information. CorEvitas regularly updates the closed claims source on a quarterly basis.

This database serves as a reliable and comprehensive source of current and longitudinal closed claims data, offering insights into patient care and the continuum of care. All claims within the dataset have undergone full adjudication, ensuring certainty that services were provided when analyzing the data. The dataset encompasses individuals from every 3-digit U.S. zip code and is maintained with strict standards for data uniformity and consistency.

One notable feature of the data source is the ability to establish links between mothers and infants based on dependents covered under the same insurance plan. This facilitates the linkage of pregnancy-related claims and birth outcomes for mothers with corresponding claims and outcomes for their infants. However, if the infant is not covered under the mother's plan, establishing a mother/infant relationship becomes challenging, limiting visibility to only those infant outcomes that were reported on the mother's claim for the birth.

9.5. Study size

The retrospective study aims to include as many eligible BRIUMVI-exposed pregnancies as possible, based on the available claims data. However, the sample size will be constrained by the number of eligible pregnancies observed in the data source.

The target sample size was calculated to adequately power the comparisons between the exposed and comparator cohorts for the primary outcome, major congenital malformations (MCMs) among live births. Assuming a baseline rate of 3%, which aligns with the Center for Disease Control and Prevention (CDC) reported prevalence at birth of birth defects in the United States, detecting a relative risk of 2.5 with 80% power would necessitate 304 live births in the BRIUMVI-exposed cohort, and 608 live births in each of the comparison cohorts (assuming a 1:2 ratio of eligible exposed to controls subjects). To account for non- live births (assuming 67% of pregnancies result in a live birth) and the percentage of pregnancies linkable to infants within the claims data (84% of live births are linkable between mother and infant), the study will need to identify 540 pregnancies eligible for the BRIUMVI-exposed cohort and 1,080 pregnancies eligible for each comparison cohort. Accounting for continuous enrollment patterns in the data (assuming 64% are continuously enrolled), roughly 844 pregnancies will need to be initially identified for the BRIUMVI-exposed cohort (and 1,688 pregnancies in each comparison cohort) to enable observation throughout the pregnancy and for 6-month prior to the pregnancy.

For each of the secondary outcomes, the minimum sample size necessary to detect a relative risk of 2.5 with 80% power was computed to be:

Table 3. Sample Size Calculations for Secondary Outcomes

Outcome	Reference Rate in Non-exposed Group	Reference	Denominator	Sample Size for the Exposed Cohort	Sample Size for Each Comparator Group
Eclampsia	0.1%	*Bartal 2022 (21)*	Pregnancies	9,555	19,110
Pre-eclampsia	4.0%	*USPST 2017 (22)*	Pregnancies	225	450
Gestational diabetes	8.3%	*Osterman 2023 (23)*	Pregnancies	101	202
Placental abruptions	1%	*Tikkanen 2010 (24)*	Pregnancies	942	1,884
SAB	11.8%	*Wu 2019 (25)*	Pregnancies	66	132
Stillbirth	0.6%	*Gregory 2021 (26)*	Live births and stillbirths	1,580	3,160
Preterm birth	8.4%	*Osterman 2022 (21)*	Singleton live births	99	198
SGA	10.0%	By definition	Live births	81	162

For the rare outcomes, stillbirths and eclampsia, assuming the study reaches the minimum sample size for the primary outcome (540 BRIUMVI-exposed pregnancies), the detectable relative risks would be 4.1 for stillbirths and 14.4 for eclampsia.

Estimating the potential size of the eligible cohort within the claims database is influenced by several factors, including the uptake of BRIUMVI in the US market, its usage among pregnant females, and its capture of BRIUMVI within the health plans encompassing the claims data set. The version of the claims database available at the time of this protocol (4.5 years of data as of December 2023) contains roughly 7,000 subjects with claims for MS and pregnancy, who are continuously enrolled for a minimum of 15 months at the time of the pregnancy. Throughout the course of the study, the database will continue to grow, capturing additional eligible subjects.

The number of BRIUMVI-exposed pregnancies within the claims data source will be monitored on an annual basis. Descriptive reports will offer insights into the number of BRIUMVI-exposed pregnancies identified in the database, the number exposed during pregnancy, and the number meeting the eligibility criteria for the study. A descriptive analysis will also be provided for the eligible pregnancies that are not linkable to the infant within the database. Monitoring the number of eligible pregnancies and live births will be done in relation to the minimum required to meet the statistical power requirements.

Annual reports will provide descriptive analyses of the eligible sample and the observed outcomes. If a sufficient number of eligible exposed pregnancies or live births are identified within the available claims data, statistical comparisons between cohorts will be feasible.

9.6. Data management

The claims data undergo adjudication and are transmitted to CorEvitas on a quarterly basis. CorEvitas will securely store the data in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations and make it accessible internally for analysis by their team, including biostatisticians and analysts. Member tokenization will be employed to ensure HIPAA-compliant linkage to other data assets, for example linkages to electronic health record (EHR) data. When necessary, CorEvitas will utilize established methods for defining pregnancy from secondary data and adhere to FDA guidance for conducting retrospective post-approval pregnancy safety studies using secondary data (17).

9.7. Data analysis

To create comparable BRIUMVI-exposed and non-BRIUMVI-exposed pregnancy and live birth cohorts, we will use propensity score (PS) methods. We will use inverse probability of treatment weighting (IPTW) to adjust for confounding of baseline factors and to preserve sample size.

For the proposed cohort comparison of pregnancies in Cohort 1 compared to those in Cohorts 2 and 3, PS models will be fit including maternal demographics, treatment, and all baseline characteristics with standardized differences >0.1 or <-0.1 in the eligible cohorts and any variable determined to be associated with pregnancy outcomes a priori. Baseline covariates with more than 5% missingness will not be considered for inclusion in the propensity score models, to avoid limiting the PS population based on data availability rather than the PS value itself. Based on preliminary analysis of the claims data, there is minimal opportunity for missingness to exceed 5% for any of the covariates.

The PS model will be a logistic regression model run on eligible pregnancies in the BRIUMVI-exposed and each comparison cohort, with BRIUMVI-exposure as the outcome in each model and the baseline covariates as the predictors. The predicted probability of each individual receiving their treatment will be predicted from the model and will be used as the propensity score. The inverse of the probabilities from the PS model will be used as weights for each pregnancy in the analysis. Separate PS models and IPTW weights will be constructed for the comparison of the BRIUMVI-exposed cohort to Cohort 2 and for the comparison of the BRIUMVI-exposed cohort to Cohort 3.

Separate PS models and corresponding IPTW weights will be computed for each comparison of interest (BRIUMVI-exposed vs. Cohort 2 and BRIUMVI-exposed vs. Cohort 3) on the subset of live births, from among the linkable eligible pregnancies, for the analyses of infant outcomes. Similar to the approach on the pregnancy cohorts, the models will include maternal and infant baseline characteristics including treatment.

9.7.1. Descriptive Analyses

For each of the three cohorts, baseline patient characteristics, including demographics, clinical and disease characteristics, and treatment history, will be summarized. The timing of exposure relative to the pregnancy period – subjects exposed at EDC vs. subjects only exposed during the pregnancy period – will also be examined. Descriptive statistics will be used to summarize continuous baseline variables, including mean and standard deviation (SD), median, 25th and 75th percentiles, as well as minimum and maximum values. Categorical variables will be

summarized using frequencies and percentages. Standardized differences will be calculated to compare the eligible (pre-IPTW) and IPTW baseline characteristics between pregnancies (and live births) in the BRIUMVI-exposed cohort and pregnancies (and live births) in each of the two BRIUMVI-unexposed cohorts.

Descriptive summary statistics will be provided for each study outcome.

Measures of Frequency

For each outcome, crude measures of prevalence rates will be reported for each of the cohorts, providing the number of eligible pregnancies and the percentage of pregnancies, or infants, experiencing the event as recorded in claims.

Annual reports will include:

- Pregnancy complications reported in aggregate as well as for each individual complication (eclampsia, pre-eclampsia, placental abruption, and gestational diabetes).
- MCMs reported in aggregate as well as for each individual system organ class (SOC).

The analysis of maternal outcomes will encompass all eligible pregnancies in each of the three cohorts. The analysis of infant outcomes will be based on infants from the segment of eligible pregnancies for which a mother-baby linkage was available, and the infant also met the inclusion criteria.

In the case of pregnancies resulting in multiple births, outcomes for each of the infants will be assessed and reported at the pregnancy level, with priority given to the severity of each outcome. For instance, if one infant in a set of twins is classified with an MCM, then the pregnancy will be reported as resulting in an MCM. This approach ensures that each outcome is appropriately weighted, taking into account the interdependence between twins or other multiples. Therefore, the reporting will be conducted at the outcome level rather than for individual infants.

A subgroup analysis will also be conducted that stratifies the pregnancies by maternal age at estimated EDC: <18, 18 to <35, 35 to<45, and ≥45 years.

Measures of Association

If the sample size of eligible pregnancies observed within the claims data is sufficient to meet the statistical power requirements, measures of association between cohorts will be calculated. Otherwise, descriptive analyses only will be provided, as described above. Based on power calculations (as described under “Study Size”), analysis of the primary outcome (MCMs) will require 196 eligible live births in the BRIUMVI- exposed cohort. The number of eligible pregnancies and live births will be assessed annually to determine the ability to analyze measures of association in the annual reports, as well as at the conclusion of the study period (in 2034).

If sample size requirements are met, regression models will be used to compare the outcomes rates between the BRIUMVI-exposed cohort and each of the comparator cohorts. Crude, unadjusted comparisons will be estimated with relative risks, and corresponding 95% confidence intervals (CIs), from log binomial models. With log binomial models, there is the potential for failed convergence of the estimated model. If the model(s) fail to converge, alternative estimation approaches to the classic log- likelihood approach via Fisher scoring will be used to estimate the RRs (e.g., Poisson regression with robust variance estimator).

Inverse probability of treatment weighting (IPTW) will be used to adjust for confounding by indication and imbalance in baseline factors within each of the pregnancy and live birth cohort comparisons. Log binomial models will be fit on the IPTW cohorts to estimate relative risks and corresponding 95% CIs. Any covariate that remains unbalanced (absolute value of the standardized difference > 0.1) across the exposure cohorts after weighting will be considered for inclusion in the regression models for the primary outcomes. Separate models will be used for comparisons of the BRIUMVI-exposed cohort to Cohort 2 (treated but unexposed to BRIUMVI) and to Cohort 3 (untreated).

If there is a sizable number of subjects with multiple pregnancies that meet the inclusion criteria, repeated measures techniques will be used to account for the correlation.

To address the primary objective, the rate of MCM's among eligible live births in the BRIUMVI-exposed cohort will be compared to the rate within each of the two comparison cohorts.

For each of the secondary objectives, the rate of each outcome will be compared between the BRIUMVI- exposed cohort and each of the two comparison cohorts, as outlined in the following table.

Unit of Analysis for Primary and Secondary Outcomes

Outcome	Unit of Analysis
Primary Outcome:	
MCM	Live Births
Secondary Outcomes – Maternal:	
Pregnancy Complications	Pregnancies
Spontaneous Abortion	Pregnancies
Stillbirth	Pregnancies
Secondary Outcomes – Infant:	
Preterm Birth	Live births
Small for Gestational Age (SGA)	Live births

If sample size permits, pregnancy complications will be analyzed separately for each individual complication (eclampsia, pre-eclampsia, placental abruption, and gestational diabetes).

MCMs will be analyzed for each system organ class, as sample size permits.

9.7.2. Missing Data

The use of secondary claims data assumes that all collected claims and required fields on the claims will be available. The absence of information will be interpreted as the absence of an event (e.g., a comorbidity or an outcome). Ensuring continuous enrollment in the contributing health plans during the observation period reduces the likelihood of missing health care encounters in the claims data. If any missing data are observed, the percentage of missing data will be reported.

Based on preliminary analysis of the claims data, there is minimal opportunity for missingness to exceed 5% for any of the covariates. If covariates exhibit <5% missingness, missing values will be imputed (using mean or median of continuous variables and mode of categorical variables) to preserve the sample size in the propensity score models. In the event that any baseline covariates exceed 5% missingness, those covariates will not be considered for inclusion in the propensity score models, to avoid limiting the population based on data availability rather than the PS value itself. Additionally, sensitivity analyses will be explored using multiple imputations on the covariates with 5% or greater missingness.

9.7.3. Statistical Analyses

The detailed methodologies for summarizing and analyzing the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be dated, filed, and maintained by the sponsor. It is important to note that the SAP may modify the plans outlined in the protocol. Any major modifications related to the definitions for the outcomes or their analyses will be reflected in a protocol amendment.

Data analyses will be performed using Stata, R/RStudio, and/or SAS.

9.7.4. Sensitivity Analyses

Sensitivity analyses will be conducted to evaluate the definitions of drug exposure at the time of pregnancy.

- The definition of exposure to BRIUMVI and other DMT treatments will be expanded to include administrations or prescriptions dispensed at any time during the 6-month period prior to EDC. This expansion removes the product-specific exposure periods based on product half-lives or recorded days supply prior to the EDC.
- Exposures will be restricted to only those that occur during pregnancy, i.e., BRIUMVI and other DMT's that were administered, or prescriptions filled, on or after the estimated EDC. This will remove the exposures that were implied based on the products' half-life extending to the estimated EDC.
- Due to the long half-life and pre-conception exposure window for BRIUMVI, a subgroup analysis will segment exposures based on the timing of exposures prior to pregnancy. For patients exposed prior to EDC, segments will be based on the most recent administration prior to EDC: 4 – 6 months prior to EDC, 2 - <4 months prior to EDC, and <2 months prior to EDC.

A sensitivity analysis will be conducted that restricts the non-BRIUMVI DMT-exposed cohort to DMT products that do not carry a fetal risk warning in the USPI. This will eliminate the following products from consideration of pregnancy exposure:

- Tascenso ODT (fingolimod)
- Gilenya (fingolimod)
- Zeposia (ozanimod)
- Ponvory (ponesimod)
- Mayzent (siponimod)

A sensitivity analysis will be conducted on pregnant subjects who were excluded from the primary analysis due to exposure to teratogenic and fetotoxic medications at EDC or during the pregnancy period. Descriptive analysis, including timing of exposure and crude outcome rates, will be provided for the BRIUMVI-exposed subjects and subjects from the two comparison groups. If the number of subjects within each group permits, measures of association will be conducted on the outcomes across the groups.

If the sample size is sufficient, further analyses can be performed by segmenting the data based on the trimester of drug exposure.

9.8. Quality control

Data storage, management and analyses will adhere to CorEvitas' standard operating procedures. These procedures encompass secure data storage, backup, and recovery measures to ensure the integrity and protection of the data. Additionally, methods will be employed to maintain and archive project documents, ensuring proper documentation and traceability. Quality-control procedures for programming will be implemented to ensure accuracy and reliability in the analysis process. These practices will ensure that data is handled and analyzed in accordance with established standards and protocols.

9.9. Limitations of the research methods

This study is subject to several limitations commonly associated with administrative claims data. The study is based on data from commercial insurance plans, so results may not be generalizable to the full population. The analysis heavily relies on diagnosis and procedure codes recorded on claims submitted to the health plan for reimbursement. Algorithms will be employed to validate the presence of specific diagnoses, such as requiring multiple occurrences of a code over time to rule out potential misdiagnoses. However, it is important to note that outcomes not coded on claims will not be visible in the analysis. Similarly, health care encounters that are not recorded or submitted on claims will also be absent from the analysis, limiting the identification of comorbidities that rely on the presence of ICD-10-CM codes. Nevertheless, the requirement of continuous enrollment in the health plans helps to minimize periods of missing data.

The validated algorithm to identify an MS diagnosis within claims data is based on a 12-month period. By using a 6-month baseline period, plus the first trimester, to identify pregnancies for subjects with MS, this study cohort will be more restrictive and may not capture some subjects with MS that would have been identified within a 12-month period.

The identification of subject characteristics such as obesity, tobacco use, alcohol use, and substance use disorders will rely on the presence of relevant ICD-10 codes documented on claims for each subject. Subjects without the relevant ICD-10 code recorded will be considered as not having the respective condition. However, it is assumed that severe conditions that could potentially impact the pregnancy would be documented by healthcare providers. Subject characteristics that require a detailed history, such as the number of prior pregnancies and births, were initially considered as potential covariates. However, due to the limited length of continual enrollment in claims data, such attributes would likely be under-reported. Therefore, they are not included in the analysis.

Potential demographic covariates such as race and ethnicity are not available in the claims data. Covariates will include measures of comorbidities and drug burden, but not the use of specific non-MS medications, to avoid correlation with comorbidities and overfitting the propensity score model.

The covariate capturing prior MS relapses will be based on a published algorithm, but the PPV of the algorithm (67.3%) may limit the ability to accurately account for prior relapses (28). The algorithm will only be applied during the 6-month baseline period (prior to EDC), which may under-represent a subject's history of relapses.

Since secondary claims data may not explicitly include pregnancy start and end dates, validated algorithms will be utilized to estimate gestational age and EDC. These algorithms will consider various factors, including diagnosis and procedure codes, the sequence of events, clinically appropriate time intervals, and code hierarchies. For instance, by utilizing codes that indicate gestational age during pregnancy or at birth, the LMP can be estimated by subtracting the gestational age from the recorded date.

The sample size of this study may be very limited. It is anticipated that exposure to BRIUMVI in most study participants will have occurred inadvertently and early in pregnancy. If monitoring of the data over time indicates that the eligible sample size is too small, additional sources of claims data may be considered. CorEvitas will monitor the available sample size each year of the study. If it becomes apparent that the growth trajectory indicates we will not reach an adequate sample size, we will reach out to vendors who have claims data that allow for a mother/baby linkage to determine the best option for adding sample. The benefit of waiting is we will be able to assess at that time how many individuals each source has in their history that meet the study requirements, and will immediately be able to add them to the population included in the study, by licensing both historic data and updates going forward. Additionally, any improvements in mother/baby linking capability and/or vendors that can support validation of signals can be evaluated at that same point in time.

The linkage of mother and infant is based on member IDs belonging to the same subscriber. If an infant is covered under a different subscriber, it may not be possible to link the infant to the mother, which can limit the identification of infant outcomes. This limitation will be mitigated by restricting the analysis of infant outcomes to the subset of pregnant mothers for whom an infant is linked and available in the claims data at the time of birth.

Published and validated algorithms for the identification of outcomes within medical claims will be used. However, not all published algorithms can be implemented in the claims database exactly as published or validated. For example, the referenced algorithms for the identification of MCMs include an option based on death in the infants' first 12 months, but death is not captured within the claims database, so the algorithms for MCMs will be based on the published criteria that only utilize ICD-10-CM codes recorded on inpatient and outpatient claims. Some outcome algorithms have been validated on ICD-9-CM codes but will be implemented on ICD-10-CM codes. Throughout the duration of the study, algorithms will be reviewed and updated to account for any modifications or newly published algorithms, which may alleviate these limitations.

Infant outcomes that are diagnosed after the infant disenrolls from the health plan will not be captured, which poses a risk of underestimating event rates.

Exposure to BRIUMVI and DMT treatments will be determined based on administration dates recorded on medical claims or dispensed dates and reported days supply on prescription claims. It is important to note that the recorded administration or dispensing dates may not necessarily correspond to the actual drug usage by the subject. However, the recorded days supply on the prescription claim provides the best estimate of when the subject had the drug on hand and was expected to be using it.

Even with the proposed methodologies, it is possible that residual confounding may be present. However, IPTW is a well-established technique to reduce residual confounding and sensitivity analyses will be conducted to ensure that inferences are stable.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

This study will be non-interventional, retrospective and will not affect the treatment of the patients. No study-related activities will be carried out prior to receiving subjects' informed consent to participate in the registry. To guarantee patient privacy, only de-identified medical data is stored in the GMSR's database and used for analysis. Local and global data protection and privacy regulations will be observed in collecting, managing, processing, and storing subject data. NxP, the sponsor of this study, will be responsible for ensuring that the study will be conducted in accordance with applicable global and local, legal and regulatory requirements, as well as the Guidelines for Good Clinical Practice (International Conference on Harmonization [GCP ICH] 1996) and the Health Insurance Portability and Accountability Act of 1996 (HIPAA), where applicable.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

As this is a non-interventional PASS using a secondary data source, the reporting of adverse events in the form of Individual Case Safety Reports is not required. Further details on how adverse events are defined, handled, and reported will be included in the relevant adverse event reporting plan (AERP).

Periodic reporting is performed in accordance with the safety assessment requirements of the respective ICH Guideline per MS drug every six months and is sent directly to the MAH who contribute to the joint financing of the registry. Centers participating in the additional documentation receive annual summary reports on the serious adverse events notified to the registry.

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.

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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: A Post-Authorization Study to Characterize the Safety of BRIUMVI (ublituximab) Use in Pregnant Patients with Multiple Sclerosis Using Data from a US Administrative Healthcare Claims Database

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

Study reference number (if applicable): TG1101-RMS404

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)	☒	☐	☐	7, 8
2.1.2 The objective(s) of the study?	☒	☐	☐	
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?	☒	☐	☐	9.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.5
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?	☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:				9.2.1
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	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)	☒	☐	☐	9.2.1

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)	☒	☐	☐	9.4
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.2.2
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?	☒	☐	☐	9.3.1

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
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
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)	☒	☐	☐	9.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.3
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.3

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)	☒	☐	☐	9.3.2

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)	☒	☐	☐	9.2, 9.3

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)	☒	☐	☐	9.3
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3
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)	☒	☐	☐	9.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Table 7
9.3.3 Covariates and other characteristics?	☒	☐	☐	Annex 3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

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
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.4

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.3.1
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.4

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.6

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?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
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

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
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
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

Table 4: End of Pregnancy Codes

Category	Code	Code Type	Description
Live birth	Z37.0	ICD-10-CM Diagnosis	Single live birth
	Z37.2	ICD-10-CM Diagnosis	Twins, both live born
	Z37.3	ICD-10-CM Diagnosis	Twins, one liveborn and one stillborn
	Z37.5x	ICD-10-CM Diagnosis	Other multiple births, all liveborn
	Z37.6x	ICD-10-CM Diagnosis	Other multiple births, some liveborn
	Z38.xx	ICD-10-CM Diagnosis	Liveborn infants according to place of birth and type of delivery
	O80	ICD-10-CM Diagnosis	Encounter for full-term uncomplicated delivery
Ectopic pregnancy	O00.xx	ICD-10-CM Diagnosis	Ectopic pregnancy
	O08.xx	ICD-10-CM Diagnosis	Complications following ectopic and molar pregnancy
	10D27ZZ	ICD-10-CM Procedure	Extraction of Products of Conception, Ectopic, Via Opening
	10D28ZZ	ICD-10-CM Procedure	Extraction of Products of Conception, Ectopic, Endo
	10T20ZZ	ICD-10-CM Procedure	Resection of Products of Conception, Ectopic, Open Approach
	10T23ZZ	ICD-10-CM Procedure	Resection of Products of Conception, Ectopic, Perc Approach
	10T24ZZ	ICD-10-CM Procedure	Resection of Ectopic POC, Perc Endo Approach
	10T27ZZ	ICD-10-CM Procedure	Resection of Products of Conception, Ectopic, Via Opening
	10T28ZZ	ICD-10-CM Procedure	Resection of Products of Conception, Ectopic, Endo
	59100	HCPCS	Surgical treatment of ectopic pregnancy: tubal or ovarian, requiring salpingectomy and/or oophorectomy, abdominal or vaginal approach

Category	Code	Code Type	Description
	59120	HCPCS	Surgical treatment of ectopic pregnancy; tubal or ovarian, requiring salpingectomy and/or oophorectomy, abdominal or vaginal approach
	59121	HCPCS	Surgical treatment of ectopic pregnancy; tubal or ovarian, without salpingectomy and/or oophorectomy
	59130	HCPCS	Surgical treatment of ectopic pregnancy; abdominal pregnancy
	59135	HCPCS	Surgical treatment of ectopic pregnancy; interstitial, uterine pregnancy requiring total hysterectomy
	59136	HCPCS	Surgical treatment of ectopic pregnancy; interstitial, uterine pregnancy with partial resection of uterus
	59140	HCPCS	Surgical treatment of ectopic pregnancy; cervical, with evacuation
	59150	HCPCS	Laparoscopic treatment of ectopic pregnancy; without salpingectomy and/or oophorectomy
	59151	HCPCS	Laparoscopic treatment of ectopic pregnancy; with salpingectomy and/or oophorectomy
Elective abortion	O04.xx	ICD-10-CM Diagnosis	Complications following (induced) termination of pregnancy
	Z33.2	ICD-10-CM Diagnosis	Encounter for elective termination of pregnancy
	10A00ZZ	ICD-10-CM Procedure	Abortion of Products of Conception, Open Approach
	10A03ZZ	ICD-10-CM Procedure	Abortion of Products of Conception, Percutaneous Approach
	10A04ZZ	ICD-10-CM Procedure	Abortion of Products of Conception, Perc Endo Approach
	10A07Z6	ICD-10-CM Procedure	Abortion of Products of Conception, Vacuum, Via Opening

Category	Code	Code Type	Description
	10A07ZW	ICD-10-CM Procedure	Abortion of Products of Conception, Laminaria, Via Opening
	10A07ZX	ICD-10-CM Procedure	Abortion of POC, Abortifacient, Via Opening
	10A07ZZ	ICD-10-CM Procedure	Abortion of Products of Conception, Via Opening
	10A08ZZ	ICD-10-CM Procedure	Abortion of Products of Conception, Endo
	01966	HCPCS	Anesthesia for induced abortion
	01964	HCPCS	Anesthesia for abortion procedures
	59840	HCPCS	Induced abortion by dilation and curettage
	59841	HCPCS	Induced abortion by dilation and evacuation
	59850	HCPCS	Induced abortion, by 1 or more intra-amniotic injections (amniocentesis- injections), including hospital admission and visits, delivery of fetus and secundines;
	59851	HCPCS	Induced abortion, by 1 or more intra-amniotic injections (amniocentesis- injections), including hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation
	59852	HCPCS	Induced abortion, by 1 or more intra-amniotic injections (amniocentesis- injections), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed intra-amniotic injection)
	59855	HCPCS	Induced abortion, by 1 or more vaginal suppositories (e.g., prostaglandin) with or without cervical dilation (e.g., laminaria), including hospital admission and visits, delivery of fetus and secundines

Category	Code	Code Type	Description
	59856	HCPCS	Induced abortion, by 1 or more vaginal suppositories (e.g., prostaglandin) with or without cervical dilation (e.g., laminaria), including hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation
	59857	HCPCS	Induced abortion, by 1 or more vaginal suppositories (e.g., prostaglandin) with or without cervical dilation (e.g., laminaria), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed medical evacuation)
	S0199	HCPCS	Medically induced abortion by oral ingestion of medication including all associated services and supplies (e.g., patient counseling, office visits, confirmation of pregnancy by HCG, ultrasound to confirm duration of pregnancy)
	S2260	HCPCS	Induced abortion, 17 to 24 weeks
	S2265	HCPCS	Induced abortion, 25 to 28 weeks
	S2262	HCPCS	Abortion for maternal indication, 25 weeks or greater
	S2266	HCPCS	Induced abortion, 29 to 31 weeks
	S2267	HCPCS	Induced abortion, 32 weeks or greater
Spontaneous abortion	O02.1	ICD-10-CM Diagnosis	Missed abortion
	O03.xx	ICD-10-CM Diagnosis	Spontaneous abortion
	01965	HCPCS	Anesthesia for missed abortion
	59812	HCPCS	Treatment of incomplete abortion, any trimester, completed surgically
	59820	HCPCS	Treatment of missed abortion, completed surgically; first trimester
	59821	HCPCS	Treatment of missed abortion, completed surgically; second trimester

Category	Code	Code Type	Description
	59830	HCPCS	Treatment of septic abortion, completed surgically
Stillbirth	Z37.1	ICD-10-CM Diagnosis	Single stillbirth
	Z37.4	ICD-10-CM Diagnosis	Twins, both stillborn
	Z37.7	ICD-10-CM Diagnosis	Other multiple births, all stillborn
	O36.4x	ICD-10-CM Diagnosis	Maternal care for intrauterine death

References: Bertoia et al (18), Moll et al (29).

Table 5: Drugs used to exclude subjects from the study cohorts*

Reason for Exclusion	Generic Name	Half Life	Pre-Conception Exposure	Reason for Exclusion
Monoclonal antibody not indicated for the treatment of MS	Rituximab	18 – 32 days	160 days prior to EDC	1st, 2nd, and 3rd trimesters
Medications contraindicated in pregnancy	Cladribine	1 day	5 days prior to EDC	1st, 2nd, and 3rd trimesters
	Teriflunomide	19 days	95 days prior to EDC	1st, 2nd, and 3rd trimesters
Drugs in the same class as Briumvi (CD20-directed cytolytic antibodies)	Ocrelizumab	26 days	130 days prior to EDC	1st, 2nd, and 3rd trimesters
	Ofatumumab	16 days	80 days prior to EDC	1st, 2nd, and 3rd trimesters

Table 6: Teratogenic and Fetotoxic Medications

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
Androgen	Methyltestosterone	6 to 8 h	2 days prior to EDC	1st, 2nd, and 3rd trimesters
	Testosterone (unmodified)	10 to 100 min	1 day prior to EDC	1st, 2nd, and 3rd trimesters
	Testosterone cypionate	8 d	40 days prior to EDC	1st, 2nd, and 3rd trimesters
	Testosterone enanthate	4.5 d	23 days prior to EDC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Mesterolone	12 to 13 h	3 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Nandrolone	144 to 288 h	30 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Oxandrolone	13.3 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Prasterone	12 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Fluoxymesterone	9.2 h	2 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
Angiotensin II receptor antagonist	Azilsartan	11 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Candesartan	9 h	2 days prior to EDC	1st, 2nd, and 3rd trimesters
	Eprosartan	20 h	5 days prior to EDC	1st, 2nd, and 3rd trimesters
	Irbesartan	11 to 15 h	4 days prior to EDC	1st, 2nd, and 3rd trimesters
	Losartan	2 h	1 day prior to EDC	1st, 2nd, and 3rd trimesters
	Olmesartan	13 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Tasosartan	Not available, but half-life of ARBs range from 1 to 3d	15 days prior to EDC	1st, 2nd, and 3rd trimesters
	Telmisartan	24 h	5 days prior to EDC	1st, 2nd, and 3rd trimesters
	Valsartan	6 h	2 days prior to EDC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
Angiotensin-converting enzyme inhibitors	Benazepril	10 to 11 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Captopril	2 h	1 day prior to EDC	1st, 2nd, and 3rd trimesters
	Cilazapril	9 h	2 days prior to EDC	1st, 2nd, and 3rd trimesters
	Enalapril	11 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Fosinopril	11.5 to 14 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Lisinopril	12 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Moexipril	12 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Perindopril	0.8 to 1 h	1 day prior to EDC	1st, 2nd, and 3rd trimesters
	Quinapril	3 h	1 day prior to EDC	1st, 2nd, and 3rd trimesters
	Ramipril	13 to 17 h	4 days prior to EDC	1st, 2nd, and 3rd trimesters
	Trandolapril	6 h	2 days prior to EDC	1st, 2nd, and 3rd trimesters
Antiarrhythmic	Amiodarone	61 d	305 days prior to EDC	1st, 2nd, and 3rd trimesters
Antibiotic	Sulfamethoxazole/ trimethoprim	8 to 10 h	90 days prior to EDC	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 EDC	1st, 2nd, and 3rd trimesters
	Dicumarol	1 to 2 d	14 days prior to EDC	At least 2 weeks prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Phenprocoumon (Fenprocoumon)	4 to 6 d	30 days prior to EDC	1st, 2nd, and 3rd trimesters
	Warfarin	40 h	14 days prior to EDC	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 EDC	1st, 2nd, and 3rd trimesters
	Valproic acid/ valproate	9 to 16 h	4 days prior to EDC	Primarily 1st trimester, but MCMs have been associated with 2nd and 3rd trimester exposures.
	Carbamazepine	12 to 65 h	14 days prior to EDC	1st, 2nd, and 3rd trimesters
	Ethotoin	3 to 9 h	2 days prior to EDC	1st, 2nd, and 3rd trimesters
	Phenytoin/ fosphenytoin	Phenytoin: 7 to 42 h Fosphenytoin: 15 min	1 day prior to EDC	1st, 2nd, and 3rd trimesters
	Primidone	10 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Topiramate	21 h	5 days prior to EDC	1st, 2nd, and 3rd trimesters
	Ethosuximide	17 to 56 h	12 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Oxcarbazepine	Oxcarbazepine: immediate-release formulations, about 2 h; tablet, 7 to 11 h Active metabolite, 10–monohydroxy: 9 to 11 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Sultiame	24 h	5 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Vigabatrin	10.5 h	3 days prior to EDC	Unknown
	Phenobarbital	70 to 140 h	30 days prior to EDC	1st, 2nd, and 3rd trimesters
	Methylphenobarbital	34 h	8 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd
Antidepressants	Paroxetine	21 h	5 days prior to EDC	1st trimester
Antifungal	Fluconazole[b]	30 h	14 days prior to EDC	2 weeks prior to conception and 1st trimester
	Flucytosine	2.4 to 4.8 h	1 day prior to EDC	1st trimester
Antineoplastic	Aminopterin	12 to 24 h	5 days prior to EDC	1st, 2nd, and 3rd trimesters
	Asparaginase	5.7 d	90 days prior to EDC	3 months prior to conception and 1st, 2nd, and 3rd trimesters
	Axitinib	2.5 to 6.1 h	7 days prior to EDC	1 week prior to conception and 1st, 2nd, and 3rd trimesters
	Brentuximab vedotin	4 to 6 d	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Methotrexate[c]	55 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Crizotinib	42 h	45 days prior to EDC	45 days prior to conception and 1st, 2nd, and 3rd trimesters
	Cytarabine	1 to 3 h	180 days prior to EDC	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	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Exemestane	24 h	30 days prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Mechlorethamine	15 min	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Mercaptopurine[c]	10 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Vinblastine	24.8 h	6 days prior to EDC	1st, 2nd, and 3rd trimesters
	Cyclophosphamide	3 to 12 h	365 days prior to EDC	12 months prior to conception and 1st trimester
	Altretamine	4.7 to 10.2 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Amsacrine	8 to 9 h	90 days prior to EDC	3 months prior to conception and 1st, 2nd, and 3rd trimesters
	Bevacizumab	480 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Bleomycin	2 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Bortezomib	40 to 193 h	210 days prior to EDC	7 months prior to conception and 1st, 2nd, and 3rd trimesters
	Busulfan	2.3 to 3.4 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Capecitabine	0.75 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Carboplatin	2.6 to 5.9 h	5 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Carmustine	15 to 75 min	90 days prior to EDC	3 months prior to conception and 1st, 2nd, and 3rd trimesters
	Cetuximab	63 to 230 h	60 days prior to EDC	2 months prior to conception and 1st, 2nd, and 3rd trimesters
	Chlorambucil	1.5 h	1 day prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Cisplatin	20 to 30 min	425 days prior to EDC	14 months prior to conception and 1st, 2nd, and 3rd trimesters
	Cladribine	1 d	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Clofarabine	5.2 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Dacarbazine	5 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Dactinomycin	36 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Dasatinib	3 to 5 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Docetaxel	11.1 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Doxorubicin	20 to 48 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Epirubicin	31.1 h +/- 6 h to 35.3 h +/- 9 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Erlotinib	36.2 h	14 days prior to EDC	2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Estramustine	10 to 20 h	5 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Etoposide	4 to 11 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Fludarabine	20 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Fluorouracil	8 to 20 min	90 days prior to EDC	3 months prior to conception and 1st, 2nd, and 3rd trimesters
	Gemcitabine	1.7 to 19.4 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Hydroxycarbamide	2 to 4.5 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Idarubicin	20 to 22 h	195 days prior to EDC	6.5 months prior to conception and 1st, 2nd, and 3rd trimesters
	Ifosfamide	15 h	4 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Imatinib	18 h	14 days prior to EDC	2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Irinotecan	6 to 12 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Lapatinib	24 h	7 days prior to EDC	1 week prior to conception and 1st, 2nd, and 3rd trimesters
	Lomustine	16 to 48 h	14 days prior to EDC	2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Melphalan	10 to 75 min	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Mitocycine	46 min	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Mitoxantrone	23 to 215 h	45 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Nelarabine	Adults: prodrug: 30 min; Ara-G: 3 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Oxaliplatin	392 h	270 days prior to EDC	9 months prior to conception and 1st, 2nd, and 3rd trimesters
	Paclitaxel	13 to 52 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Pemetrexed	3.5 h	1 day prior to EDC	Unknown
	Pembrolizumab	22d	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Pentostatin	5.7 h	2 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Procarbazine	(IV), approximately 10 min	1 day prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Raltitrexed	260 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Sorafenib	25 to 48 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Streptozocin	Systemic: 35 min unchanged drug; 40 h metabolites	30 days prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Sunitinib	40 to 60 h	30 days prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Tegafur	6.7 to 11.3 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Temozolomide	1.8 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Teniposide	5 h	1 day prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Thioguanine	80 min	1 day prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Thiotepa	1.4 to 3.7 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Topotecan	2 to 3 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Vincristine	85 h	180 days prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Vindesine	2.9 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Vinorelbine	27.7 to 43.6 h	10 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Lenalidomide	3 h	28 days prior to EDC	4 weeks prior to conception and 1st, 2nd, and 3rd trimesters
Antithyroid	Propylthiouracil	1 to 2 h	1 day prior to EDC	1st and 2nd trimesters
	Methimazole	4.9 to 5.7 h	2 days prior to EDC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Radioiodine	192 h	365 days prior to EDC	6 to 12 months prior to conception and 1st, 2nd, and 3rd trimesters
Antiviral	Ribavirin	12 d	60 days prior to EDC	1st, 2nd, and 3rd trimesters
Endothelin receptor antagonist	Ambrisentan	15 h	4 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Bosentan	5 to 8 h	2 days prior to EDC	2 days prior to conception and 1st trimester
	Macitentan	16 to 48 h	10 days prior to EDC	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 EDC	1st, 2nd, and 3rd trimesters
Immunomodulatory agent	Mycophenolate mofetil	16 h	4 days prior to EDC	1st, 2nd, and 3rd trimesters
	Thalidomide	5 to 7 h	30 days prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Penicillamine	2 to 4 h	1 day prior to EDC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Azathioprine[c]	5 h	1 day prior to EDC	Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy"
	Leflunomide	432 to 456 h	730 days prior to EDC	2 years prior to conception and 1st, 2nd, and 3rd trimesters
	Mycophenolic acid	8 to 16 h	4 days prior to EDC	Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy"
	Pomalidomide	7.5 to 9.5 h	2 days prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
Mood stabilizer	Lithium	24 h	5 days prior to EDC	1st, 2nd, and 3rd trimesters
NSAID	Aspirin	2 to 30 h	7 days prior to EDC	2nd and 3rd trimesters
	Ibuprofen	1.9 to 2.2 h	1 day prior to EDC	2nd and 3rd trimesters
	Indomethacin	4.5 h	1 day prior to EDC	2nd and 3rd trimesters
	Naproxen	12 to 17 h	4 days prior to EDC	2nd and 3rd trimesters
Prostaglandins analog	Misoprostol	20 to 40 min	30 days prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
Retinoid	Alitretinoin	9 h	30 days prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Tretinoin	0.5 to 2 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Vitamin A	TERIS only notes "long half-life"; 75 days per google search	365 days prior to EDC	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	1095 days prior to EDC	3 years prior to stopping treatment and throughout pregnancy, especially 1st trimester
	Etretinate	120 d	1095 days prior to EDC	3 years prior to stopping treatment and throughout pregnancy, especially 1st trimester
	Isotretinoin	10 to 12 h	30 days prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Tazarotene	18 h	4 days prior to EDC	1st, 2nd, and 3rd trimesters
	Retinol	2 to 9 h	365 days prior to EDC	12 months prior to conception and 1st trimester
Steroid	Danazol	9.7 to 23.7 h	5 days prior to EDC	1st, 2nd, and 3rd trimesters
Tetracycline antibiotic	Demeclocycline	10 to 17 h	4 days prior to EDC	2nd and 3rd trimesters
	Oxytetracycline	6 to 11 h	3 days prior to EDC	2nd and 3rd trimesters
	Tetracycline	6 to 11 h	3 days prior to EDC	2nd and 3rd trimesters
	Chlortetracycline	5.6 h	2 days prior to EDC	2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure[a]	Drug Class
	Doxycycline	18 to 22 h	5 days prior to EDC	2nd, and 3rd trimesters
	Methacycline	14 to 22 h	5 days prior to EDC	2nd, and 3rd trimesters
	Minocycline	11 to 24.31 h	6 days prior to EDC	2nd, and 3rd trimesters
	Tigecycline	27 to 43 h	9 days prior to EDC	2nd, and 3rd trimesters
Other	Methylene blue	24 h	5 days prior to EDC	1st, 2nd, and 3rd trimesters
	Riociguat	12 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Sparsentan	9.6 h	2 days prior to EDC	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.

Note: The drugs used to exclude subjects from the study cohorts will be monitored and updated throughout the course of the study.

Table 7: Outcome definitions, codes, and referenced algorithms

Code	Code Type	Description	Algorithm / PPV
Pregnancy Complications:			
Pre-eclampsia (*reference Chomistek et al (30)*			
O11.x	ICD-10-CM Diagnosis	Pre-existing hypertension with pre-eclampsia	At least one claim from an inpatient stay

Code	Code Type	Description	Algorithm / PPV
			PPV = 78.3%
O14.xx	ICD-10-CM Diagnosis	Pre-eclampsia	
Eclampsia *(reference Labgold et al (31)*			
O15.xx	ICD-10-CM Diagnosis	Eclampsia	At least one diagnosis code PPV = 100%
Placental abruption *(reference He et al 2020 (32)*			
			At least one code on an inpatient claim or other claim during the delivery stay PPV = 92%*
O45.xx	ICD-10-CM Diagnosis	Premature separation of placenta [abruptio placentae]	
Gestational diabetes *(reference Stanhope et al (33)*			
O24.41x	ICD-10-CM Diagnosis	Gestational diabetes mellitus in pregnancy	At least one code during the delivery hospitalization PPV = 85.6%
O24.42x	ICD-10-CM Diagnosis	Gestational diabetes mellitus in childbirth	
O24.43x	ICD-10-CM Diagnosis	Gestational diabetes mellitus in the puerperium	
Spontaneous Abortion *(reference Chomistek et al (30)*			
O02.1	ICD-10-CM Diagnosis	Other abnormal products of conception - Missed abortion	At least one claim PPV = 84.7%
O03.xx	ICD-10-CM Diagnosis	Spontaneous abortion	
01965	CPT code	Anesthesia for incomplete or missed abortion procedures	
59800-59811	CPT code	Treatment of spontaneous abortion	
Stillbirth *(reference Andrade et al 2021 (34)*			
Z37.1	ICD-10-CM Diagnosis	Single stillbirth	At least one code plus gestational age >=20 weeks (Z3A.20-Z3A.49) recorded in the prior 28 days, and
Z37.3	ICD-10-CM Diagnosis	Twins, one liveborn and one stillborn	
Z37.4	ICD-10-CM Diagnosis	Twins, both stillborn	

Code	Code Type	Description	Algorithm / PPV
Z37.6x	ICD-10-CM Diagnosis	Other multiple births, some liveborn	at least two codes on the outcome date or no other pregnancy outcome codes on that date PPV = 82.5%
Z37.7	ICD-10-CM Diagnosis	Other multiple births, all stillborn	
O31.0x	ICD-10-CM Diagnosis	Papyraceous fetus	
O36.4x	ICD-10-CM Diagnosis	Maternal care for intrauterine death	
P95	ICD-10-CM Diagnosis	Stillbirth	
Preterm Birth *(reference Chomistek et al (30)*			
O60.10	ICD-10-CM Diagnosis	Preterm labor with preterm delivery, unspecified trimester	At least one claim PPV = 92.3%
O60.12	ICD-10-CM Diagnosis	Preterm labor second trimester with preterm delivery second trimester	
O60.13	ICD-10-CM Diagnosis	Preterm labor second trimester with preterm delivery third trimester	
O60.14	ICD-10-CM Diagnosis	Preterm labor third trimester with preterm delivery third trimester	
P07.2x	ICD-10-CM Diagnosis	Extreme immaturity of newborn	
P07.3x	ICD-10-CM Diagnosis	Preterm [premature] newborn [other]	
Small for Gestational Age *(reference He et al 2020 (32)*			
			At least one code recorded on a maternal or infant inpatient or other therapy claims from delivery to delivery + 30 Days PPV = 92%*
P05.0x	ICD-10-CM Diagnosis	Newborn light for gestational age	
P05.1x	ICD-10-CM Diagnosis	Newborn small for gestational age	
P05.9x	ICD-10-CM Diagnosis	Newborn affected by slow intrauterine growth,	
Major Congenital Malformations *(reference Kharbanda ([20] – PPV=76%-100%)*			
Central nervous system			

Code	Code Type	Description	Algorithm / PPV
Q01.x	ICD-10-CM Diagnosis	Neural tube defects: Encephalocele, Cranial Meningocele, Encephalomyelocele	1 inpatient diagnosis or 2 outpatient diagnoses or (1 diagnosis and death in first year)**
Q05.x, Q07.01, Q07.03	ICD-10-CM Diagnosis	Spina Bifida	
Q02	ICD-10-CM Diagnosis	Microcephaly	1 diagnosis at birth or 3 diagnoses in first 3 months or (1 diagnosis and death in the first year)**
Q04.2	ICD-10-CM Diagnosis	Holoprosencephaly	2 outpatient diagnoses or (1 diagnosis and death in first year)**
Eye			
Q11.1, Q11.2	ICD-10-CM Diagnosis	Anophthalmia, Microphthalmia	2 outpatient diagnoses or (1 diagnosis and death in first year)**
Q12.0, Q12.3, Q12.4, Q12.8	ICD-10-CM Diagnosis	Cataracts and Other Lens Defects	
Ear			
Q16.0, Q16.1, Q17.2		Anotia, Microtia	2 outpatient diagnoses or (1 diagnosis
Cardiac			
Q20.0, Q20.1, Q20.2, Q20.3-Q20.5, Q21.2-Q21.4, Q22.5- Q22.6, Q23.0, Q23.4, Q25.1, Q25.2x, Q25.3, Q25.41, Q25.42, Q25.5, Q26.2	ICD-10-CM Diagnosis	Severe cardiac defects: Single ventricle, tricuspid atresia, ebstein anomaly, hypoplastic left heart, hypoplastic right heart, common truncus, transposition, atrioventricular septal defects, tetralogy of fallot, aortic valve atresia or stenosis, coarctation, total anomalous pulmonary venous return, double outlet right ventricle, double outlet left ventricle	2 inpatient diagnoses or 1 inpatient and 1 outpatient diagnosis or (1 diagnosis and death in first year)**

Code	Code Type	Description	Algorithm / PPV
Q20.8, Q20.9, Q21.0, Q21.8, Q21.9, Q22.0, Q22.3, Q22.4, Q26.3, Q26.4, Q89.3	ICD-10-CM Diagnosis	Other cardiac defects: Septal defects, heterotaxy, pulmonary valve atresia, tricuspid stenosis, partial anomalous pulmonary venous return	2 diagnoses or (1 diagnosis and death in first year)**
Orofacial/respiratory			
Q30.0	ICD-10-CM Diagnosis	Choanal atresia	2 outpatient diagnoses or (1 diagnosis and death in first year)**
Q35.1-Q35.5, Q35.9, Q36.x, Q37.x	ICD-10-CM Diagnosis	Cleft lip and/or cleft palate	1 inpatient diagnosis or 2 outpatient diagnoses or (1 diagnosis and death in first year)**
Gastrointestinal			
Q44.2	ICD-10-CM Diagnosis	Biliary atresia	1 inpatient diagnosis or 2 outpatient diagnoses or (1 diagnosis and death in first year)**
Q41.x, Q42.x	ICD-10-CM Diagnosis	Intestinal atresia or stenosis	1 inpatient diagnosis or 2 outpatient diagnoses or (1 diagnosis and death in first year)**
Q39.0-Q39.3	ICD-10-CM Diagnosis	Esophageal atresia with or without tracheoesophageal fistula	2 outpatient diagnoses or 1 inpatient and 1 outpatient diagnosis or (1 diagnosis and death in first year)**
Q40.0	ICD-10-CM Diagnosis	Pyloric stenosis	1 inpatient diagnosis or (1 diagnosis and death in first year)**
Q64.1x	ICD-10-CM Diagnosis	Bladder exstrophy	1 inpatient diagnosis by 3 months of age and 1 outpatient diagnosis by 1 year or (1 diagnosis and death in first year)**
Genitourinary/renal			

Code	Code Type	Description	Algorithm / PPV
Q54.0-Q54.3, Q54.8, Q54.9	ICD-10-CM Diagnosis	Hypospadias	2 outpatient diagnoses or (1 diagnosis and death in first year)**; males only
Q61.4	ICD-10-CM Diagnosis	Renal dysplasia	2 outpatient diagnoses or (1 diagnosis and death in first year)**
Q60.0-Q60.6	ICD-10-CM Diagnosis	Renal agenesis or hypoplasia	1 inpatient diagnosis and 1 outpatient diagnosis or (1 diagnosis and death in first year)**
Q64.2	ICD-10-CM Diagnosis	Posterior urethral valves	2 outpatient diagnoses or (1 diagnosis and death in first year)**; males only
Musculoskeletal			
Q79.3	ICD-10-CM Diagnosis	Gastroschisis	1 inpatient diagnosis or 2 outpatient diagnoses or (1 diagnosis and death in first year)**
Q79.2	ICD-10-CM Diagnosis	Omphalocele	1 inpatient diagnosis by 3 months of age or (1 diagnosis and death in first year)**
Q79.0	ICD-10-CM Diagnosis	Congenital diaphragmatic hernia	1 inpatient diagnosis by 3 months of age or (1 diagnosis and death in first year)**
Q71.0x - Q71.6x, Q71.89x, Q71.9x, Q72.0x – Q72.7x, Q72.89x, Q72.9x, Q73.x	ICD-10-CM Diagnosis	Limb deficiency	1 inpatient or 2 outpatient diagnoses and 1 diagnosis within 3 months or (1diagnosis and death in first year)**

*PPV in the referenced algorithm was based on ICD-9-CM codes; but algorithm will be implemented on ICD-10-CM codes.
**Death is not captured within the claims data, so this portion of the algorithm may not be implemented, unless death is otherwise identifiable in the claims data.

Approval Page

Project Title: A Post-Authorization Study to Characterize the Safety of BRIUMVI (ublituximab) Use in Pregnant Patients with Multiple Sclerosis Using Data from a US Administrative Healthcare Claims Database

Principal Investigator: Diego Wyszynski, MD, MHS, PhD

Version: 1.0

Version Date: 21 Mar 2024

_____ 21 Mar 2024_____

Date

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