BRIUMVI® Pregnancy Registry: A Prospective Study of Pregnancy and Infant Outcomes in Patients Treated with BRIUMVI (ublituximab-xiiy)

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OBJECTIVES

- To present the design of a post-marketing study evaluating maternal, fetal, and infant outcomes of pregnant individuals with MS exposed to ublituximab at any time during pregnancy, including the 6 months prior to the date of conception.

OVERVIEW IN BRIEF

- Study population to include 2 internal cohorts of pregnant individuals with MS and 1 "external cohort" representing the general population in the US.
  - Internal cohorts: 1) pregnant individuals with MS exposed to ublituximab at any time during pregnancy; 2) pregnant individuals with MS not exposed to ublituximab or other anti-CD20 mAbs at any time during pregnancy but who may be exposed to other DMTs for the treatment of MS.
  - External cohort: Background rates from population-based surveillance systems or the published literature.
- **Exposure is defined as maternal infusion with ublituximab in the 6 months prior to LMP or during pregnancy**
- Primary outcomes: prevalence rate of major congenital malformations
- Secondary outcomes include: minor congenital malformations, gestational hypertension, pre-eclampsia, eclampsia, gestational diabetes, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm births, postnatal growth deficiency, infant developmental delays, infant serious or opportunistic infections, and infant hospitalizations

CONCLUSIONS

- This registry will provide information on maternal, fetal, and infant outcomes following exposure to ublituximab during pregnancy to support evidence-based clinical decision making for women of child-bearing age with MS.

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BACKGROUND

- Multiple sclerosis (MS) commonly affects women of child-bearing age.[1-2]
- Increased understanding of how individual disease modifying therapies (DMTs) might impact women with MS and their infants during pregnancy and post-partum is needed.[3-4]
- BRIUMVI (ublituximab-xiiy) is a glycoengineered monoclonal IgG1 antibody targeting CD20 and is approved for the treatment of relapsing MS. Currently, there are no adequate and well-controlled clinical studies of ublituximab in pregnant individuals, and available human data on exposure during pregnancy are insufficient to inform risk analysis.[5]

METHODS

- The BRIUMVI Pregnancy Registry is a prospective, observational cohort study designed to evaluate the association between ublituximab exposure during pregnancy (including 6 months prior to conception) and subsequent maternal, fetal, and infant outcomes.
- A Single-Site Virtual Coordinator Center (VRCC) will support enrollment and data collection. Participants may self-enroll through a web-based application or by calling the VRCC
- Enrolled pregnant individuals and the HCPs involved in their care or the care of their infants, if applicable, will serve as the data reporters to the registry.
- Pregnancy outcomes will be assessed throughout pregnancy, with data collection occurring at enrollment, the end of the second trimester, and at pregnancy outcome. Infant outcomes will be assessed throughout the infant's first year of life, with active data collection by the registry occurring at 4 and 12 months after delivery.

Number of Participants (Planned):

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

Primary Objective:

- To compare the prevalence rate of MCMs between pregnant individuals with MS who are exposed to BRIUMVI during pregnancy, or up to 6 months prior to pregancy, versus pregnant individuals with MS who are unexposed to BRIUMVI or other anti-CD20 monoclonal antibodies during pregnancy but who may be exposed to other products for the treatment of MS.

Secondary Objectives:

- To compare the prevalence rates of the secondary outcomes between the cohorts
- To compare the prevalence rates of the primary and secondary outcomes in the exposed cohort to rates in the general population from the published literature.

Study Duration and Follow-Up:

- Enrollment of individuals in the registry and data collection are expected to occur over approximately 10 years.
- For each enrolled pregnant individual, participation will begin at enrollment and end at pregnancy outcome (if fetal loss) or 12 months after pregnancy outcome (if live birth).

Study Population and Eligibility Criteria:

- The study population will include 2 internal cohorts of pregnant individuals with MS and 1 "external cohort" representing the general population in the US. **(Table 1, Table 2, Table 3)**
- Internal study population: pregnant individuals 15–50 years of age who provide consent to participate in the study, agree to medical releases for their HCPs to provide data to the registry, and meet the criteria for inclusion into 1 of the following cohorts:
  - Exposed cohort: Pregnant individuals with MS who are exposed to BRIUMVI® at any time during pregnancy including up to 6 months prior to conception
  - Unexposed cohort: Pregnant individuals with MS who are not exposed to BRIUMVI® or other anti-CD20 monoclonal antibodies at any time during pregnancy but who may be exposed to other products for the treatment of MS.
- External study population: The registry will use background rates from population-based surveillance systems or the published literature as external comparators.
- Individuals will be eligible for enrollment but excluded from the analysis population if the pregnancy outcome occurred prior to first contact with the registry, or if they have been exposed to known teratogens and/or investigational medications during pregnancy, but may be included in supplementary analyses.
- **Table 3** shows the study outcomes for which reliable external comparators have been identified. Other appropriate external comparators may be identified during the study and used along with published literature to obtain background data for the maternal, fetal, and infant outcomes evaluated.

Table 1. Key Eligibility Criteria: Internal Study Population Exposed Cohort

Cohort	Inclusion Criteria	Exclusion Criteria for Enrollment	Exclusion Criteria for Analysis Population
Exposed[1] cohort: Pregnant individuals diagnosed with MS who are exposed to BRIUMVI at any time during pregnancy	• Individuals 15-50 years of age • Currently or recently (within 1 year of pregnancy outcome) pregnant • Diagnosis of MS • Consent to participate • Authorization for the HP(s) to provide data to the registry • Exposure[1] to at least 1 dose of BRIUMVI at any time during pregnancy	• Prior to enrollment, exposure[2] to other anti-CD20 monoclonal antibodies at any time during pregnancy	• Occurence of pregnancy outcome prior to first contact with the VRCC (retrospectively enrolled) • After enrollment, exposure to anti-CD20 monoclonal antibodies other than BRIUMVI at any time during pregnancy • Exposure[2] to unknown teratogens and/ or investigational medications during pregnancy • Lost to follow up

Abbreviations: HCP = healthcare provider; MS = multiple sclerosis; VRCC = virtual research coordination center . [1]Exposure is defined as bodily uptake of any dose of BRIUMVI at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within 6 months of the date of conception). [2]Exposure is defined as bodily uptake of any dose of anti-CD20 monoclonal antibody at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within 5 half-lives of the date of conception).

Table 2. Key Eligibility Criteria: Internal Study Population Unexposed Cohort

Cohort	Inclusion Criteria	Exclusion Criteria for Enrollment	Exclusion Criteria for Analysis Population
Unexposed[1] cohort: Pregnant individuals diagnosed with MS who are NOT exposed to BRIUMVI or any other anti-CD20 monoclonal antibody at any time during pregnancy, but who may be exposed to other products for the treatment of MS	• Individuals 15-50 years of age • Currently or recently (within 1 year of pregnancy outcome) pregnant • Diagnosis of MS • Consent to participate • Authorization for the HP(s) to provide data to the registry • No exposure[1] to BRIUMVI at any time during pregnancy or in the 6 months prior to conception	• Prior to enrollment, exposure[2] to other anti-CD20 monoclonal antibodies at any time during pregnancy	• Occurence of pregnancy outcome prior to first contact with the VRCC (retrospectively enrolled) • After enrollment, exposure[2] to anti-CD20 monoclonal antibodies other than BRIUMVI at any time during pregnancy • Exposure to unknown teratogens and/ or investigational medications during pregnancy • Lost to follow up

Abbreviations: HCP = healthcare provider; MS = multiple sclerosis; VRCC = virtual research coordination center. [1]Exposure is defined as bodily uptake of any dose of BRIUMVI at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within 6 months of the date of conception). [2]Exposure is defined as bodily uptake of any dose of anti-CD20 monoclonal antibody at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within 5 half-lives of the date of conception).

Table 3. Key Eligibility Criteria: External Comparators

Outcomes	External Comparator	Current Rate	Reference	Denominator
MCM	CDC MACDP	3.0%	CDC2008	Live Births
Gestational hypertension	US Birth Certificate Data	6.5%	Butwick 2020	Live Births
Pre-eclampsia	CDC National Hospital Discharge Summary	3.4%	Ananth 2013	Pregnant Individuals
Eclampsia	US Birth Certificate Data	0.3%	Butwick 2020	Live Births
Gestational diabetes	CDC NVSS	6.9%	Martin 2021	Live Births
SAB	Right from the Start	11.8%	Wu 2019	Pregnant Individuals
Stillbirth	CDC NVSS	0.6%	Gregory 2021	Live Births and Stillbirths
Elective termination	Guttmacher Institute	18.4%	Jones 2019	Live Birth and Abortions
Pre-term birth	CDC NVSS	8.4%	Osterman 2022	Singleton Live Births
SGA	N/A	10% by definition	By definition	Singleton Live Births
Postnatal growth deficiency	N/A	10% by definition	By definition	Singleton Live Births
Infant developmental delay	Early Childhood Longitudinal Study	13%	Rosenberg 2008	Infants

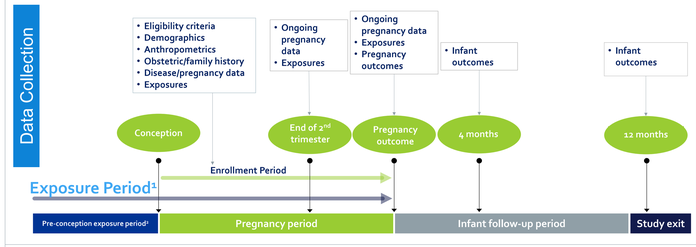
Abbreviations: CDC = Centers for Disease Control and Prevention; MACDP = Metropolitan Atlanta Congenital Defects Program; MCM = major congenital malformation; N/A = not applicable; NVSS = National Vital Statistics System; SAB = spontaneous abortion; SGA = small for gestational age.

RESULTS

Study Design and Data Collection:

- An overview of the data collection process is shown in **Fig 1**.
- Data collection begins at enrollment with cumulative data throughout the pregnancy collected at 3 timepoints:
  - Enrollment
  - End of the second trimester (approximately 26 gestational weeks)
  - At pregnancy outcome (live birth or fetal loss).
- For live-born infants, data from pediatric visits at 4 and 12 months of age will be collected at:
  - 4 months and 12 months after delivery.
- Data-collection efforts will be identical for all enrolled pregnant individuals regardless of exposures and study cohort assignment.
- HCPs who serve as reporters to the registry will be instructed to transcribe data that are readily available in the patients' medical records into the data-collection form.
- The primary outcome is the prevalence rate of major congenital malformations observed between the 2 internal cohorts. **(Fig. 2)**.
- Secondary outcomes will include both pregnancy and infant outcomes as shown in **Fig. 2**.

Figure 1: The pregnancy registry collects data documented in the patient chart



[1]If a participant is exposed during this period, she will be considered exposed during pregnancy
[2]For the BRIUMVI cohort defined as within 6 months of the date of conception. For the unexposed cohort, defined as within 5 half-lives of the date of conception

Figure 2. Primary and Secondary Outcomes

Primary Outcomes	Secondary Outcomes (Pregnancy)	Secondary Outcomes (Infant)
• Major Congenital Malformations	• Minor congenital malformations	• Preterm birth
	• Gestational hypertension	• Small for gestational age (SGA)
	• Pre-eclampsia	• Postnatal growth deficiency
	• Eclampsia	• Infant developmental delay
	• Gestational diabetes	• Infant serious or opportunistic infections
	• Spontaneous Abortion (SAB)	• Infant hospitalizations
	• Stillbirth	
	• Elective termination	

Sample Size:

- Sample size calculations were performed for the outcomes of interest using the Fisher's exact conditional test with Walters normal approximation method, and assuming a power of 80%, a 2-sided α level of 0.05, an equal number of individuals in each cohort, and observed prevalence rates of the outcomes of interest in the unexposed cohort equivalent to reference comparator rates in the general population.
- 265 live births in the analysis population of each cohort are needed to detect a 3-fold increase in the prevalence of MCM between cohorts, or an RR of 3.
- It was assumed that 90% of enrolled individuals would be exposed in the first trimester, 90% of enrolled pregnancies would result in a live birth, and 10% of enrolled individuals would be excluded from the analysis population
- Given these assumptions, to attain 265 live births per cohort, 364 pregnant individuals would need to be enrolled in each of the 2 cohorts of the study population, and a total of 728 individuals would need to be enrolled in the registry.
- This sample size will afford the study the ability to detect a 3-fold increase in the prevalence of the primary outcome, MCMs, in the BRIUMVI-exposed cohort, with meaningful confidence (95% confidence level).