A Post-Marketing Study Evaluating the Presence and Concentration of BRIUMVI® (ublituximab-xiiy) in Breastmilk (PROVIDE)

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OBJECTIVES

- To present the design of a post-marketing study characterizing the transfer of ublituximab in breastmilk of lactating women with RMS receiving ublituximab.

OVERVIEW IN BRIEF

- The study aims to enroll up to 16 breastfeeding women to obtain 10 completed mother-infant dyads.
- The primary endpoint is milk pharmacokinetic parameters (area under the concentration-time curve, concentration at end of dosing interval, maximum observed concentration, time of first occurrence of maximum concentration).
- Secondary endpoints include amount of ublituximab excreted in milk, fraction of dose excreted in milk, estimates of infant exposure, and infant AEs.
- Relative infant dose will be determined by dividing infant dose by maternal dose/maternal bodyweight multiplied by 100.

CONCLUSIONS

- This study will generate data about the transfer of ublituximab in human breastmilk to support evidence-based clinical decision making for lactating women with RMS.

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Study details can be found on: https://www.clinicaltrials.gov/study/NCT06143514

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BACKGROUND

- Increased inflammatory activity (clinical and radiologic) has been demonstrated in women with multiple sclerosis (MS) during the first post-partum trimester.[1-3]
- Exclusive breastfeeding post-delivery is often recommended for its general benefits and may reduce relapse risk in people with mild to moderate MS but not in people with highly active disease.[2, 5-6]
- The use of effective disease modifying therapies (DMTs) in combination with breastfeeding may further minimize risk of post-partum inflammatory activity.[2-7]
- Understanding the capacity for DMT transfer in breastmilk may have important clinical implications for both mothers and infants.
- Studies of IgG1 antibodies have demonstrated very low transfer in breastmilk, with concentrations unlikely to be orally bioavailable or pharmacologically relevant.[8-11]
- BRIUMVI® (ublituximab-xiiy) is a glycoengineered monoclonal IgG1 antibody targeting CD20 and approved for treatment of relapsing MS (RMS). No data are currently available to describe the concentration of ublituximab in human milk.[12]

METHODS

- This multicenter, prospective, post-marketing study is designed to assess the presence and concentration of ublituximab in breastmilk of lactating women with RMS.
- The study will include both breastfeeding adults (18 years or older) with RMS receiving ublituximab who provide consent to participate and meet the criteria for inclusion, as well as their infants. **(Table 1 and 2)**
- Milk collection will occur at a series of 14 timepoints over 90 days: 1 pre-infusion (spot) and 13 post-infusion: Day 1 (0-4 hrs, 4-8 hrs, 8-12 hrs, 12-18 hrs, 18-24 hrs), and spot collection on Days 2, 3 ,7, 10, 14, 28, 60, and 90. **(Fig. 1)**
- Estimates of exposure for breastfed infants and infant adverse events (AEs) will also be collected. **(Fig. 1)**

Table 1. Key Inclusion Criteria

Maternal	Infant
Independently decided to be treated with ublituximab prior to consent	Gestational age at delivery ≥35 weeks
Diagnosis of RMS to include CIS, RRMS, and active SPMS	Birthweight >10th percentile
Established lactation in the index post-partum period (breastfeeding or pumping for at least 2 weeks at time of Day 1 to ensure mature milk production)	Weight >10th percentile as reported by the mother at the time of enrollment
Willing to breastfeed or pump during the study period and exclusively pump for 24-hour period of breastmilk collection Day 1 post IV dose	
Plans to give infant breastmilk for at least duration of study	

Abbreviations: RMS = relapsing multiple sclerosis; CIS = clinically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; IV = intravenous

Table 2. Key Exclusion Criteria

Maternal	Infant
Received any investigational compound or approved biologic within 30 days or 5 half-lives (whichever is longer) other than ublituximab	Any abnormality noted or clinically significant medical condition at the time of screening that may make implementation of the protocol or interpretation of the trial difficult or would put the infant at risk
Any active infection or other condition that would prevent breastfeeding	Infant has any abnormality that may interfere with breastfeeding or milk absorption
History of breast implants, breast augmentation, or breast reduction surgery, or mastectomy that significantly impacts breastfeeding	
Current use of drugs known to transfer to the breastmilk and with established or potential deleterious effects for the infant, including but not limited to aspirin, tetracyclines or fluoroquinolones	

RESULTS

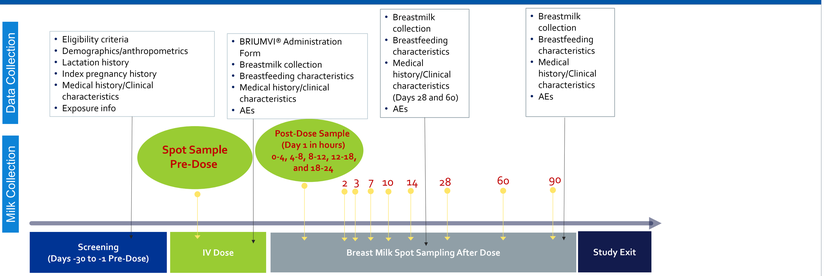
Primary Objective:

To characterize the presence and concentration of ublituximab in breast milk of lactating women with RMS who receive ublituximab

Secondary Objective:

To report estimates of exposure for breastfed infants and infant AEs

Figure 1. PROVIDE Study Design



Study Design:

- US based, post-marketing lactation study (milk only).
- Single-Site Virtual Coordinator Center will support enrollment and data collection. Participants may self-enroll through a web-based application or by calling the VRCC.
- Enrolled breastfeeding participants, prescribing HCPs, and infusion clinic staff will serve as data reporters.
- Central Lab will provide breastmilk pump (as needed) and milk collection kits directly to participant's home.
- Aims to enroll up to 16 breastfeeding women to obtain 10 completed mother-infant dyads. Completed study dyads are defined as those who contribute all required milk samples.
- Study plan to fully enroll within one year of study initiation (initiated April 2024).
- Eligible to enroll into the study within 30 days prior to any scheduled post-partum 450 mg dose of ublituximab.
- Milk Collection: 14 timepoints; 1 pre-dose and 13 post-dose over a period of 90 days **(Figure 1).**
- Estimates of exposure for breastfed infants and infant AEs will also be collected. Relative infant dose will be determined by dividing infant dose by maternal dose/maternal body weight multiplied by 100 **(Figure 2).**
- During spot collection, the participant will be instructed to pump all milk (pump to empty) from both breasts for a single pooled sample.

Figure 2. Primary and Secondary Endpoints

Primary	Secondary
Milk Pharmacokinetic Parameters:	**Amount of ublituximab excreted in milk**
• Area under the concentration-time curve	**Fraction of dose excreted in milk**
• Concentration at end of dosing interval	**Estimates of infant exposure (infant dosage and relative infant dosage)**
• Maximum observed concentration	**Infant AEs**
• Time of first occurrence of maximum concentration	

Statistical Analysis Plan:

- Demographic and baseline characteristics will be summarized with descriptive statistics for all participants (maternal and infant). Maternal and infant AEs will also be summarized with descriptive statistics. Summary statistics (number of participants, mean, standard deviation [SD], median, minimum and maximum) will be calculated for continuous variables (e.g., age and weight) and the number and percentage of individuals within each category will be presented for categorical variables.
- Concentrations of ublituximab in breastmilk will be summarized at scheduled timepoints using descriptive statistics. Additional statistical analysis will be conducted as appropriate. Milk pharmacokinetic (PK) parameters of ublituximab will be derived using non-compartmental analysis methods. The PK parameters of ublituximab will be determined using the concentration-time data for all evaluable participants. Actual sampling times for spot samples and actual mid-point sampling times for pooled samples rather than scheduling sampling times will be used in all computations involving sampling times.