# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761238Orig1s000

# OTHER REVIEW(S)

**Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**
**Epidemiology: ARIA Sufficiency**

| | |
|---|---|
| Date: | December 14, 2022 |
| Reviewer: | Silvia Perez-Vilar, PhD, PharmD<br>Division of Epidemiology I |
| Team Leader: | Kira Leishear, PhD, MS<br>Division of Epidemiology I |
| Division Director: | CAPT Sukhminder K. Sandhu, PhD, MPH, MS<br>Division of Epidemiology I |
| Subject: | ARIA Sufficiency Memo for Pregnancy Safety Concerns |
| Drug Name: | BRIUMVI (Ublituximab) |
| Application Type/Number: | BLA 761238 |
| Applicant/sponsor: | TG Therapeutics |
| TTT Record #: | 2022-511 |

**Expedited ARIA Sufficiency for Pregnancy Safety Concerns**

## 1. BACKGROUND INFORMATION

### 1.1. Medical Product

Ublituximab (BRIUMVI, TG Therapeutics) is a recombinant IgG1 chimeric, glycoengineered monoclonal antibody targeting the CD20 antigen. The proposed indication is the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Ublituximab is not currently approved in the United States or elsewhere for any indication. The over 20 products approved for the treatment of relapsing forms of multiple sclerosis include two other anti-CD20 monoclonal antibodies: ocrelizumab (OCREVUS) and ofatumumab (KESIMPTA). Ocrelizumab is also approved for the treatment of primary progressive multiple sclerosis. The precise mechanism by which anti-CD20 therapies exert therapeutic effects in multiple sclerosis is unknown, but is presumed to involve binding to CD20 on B-lymphocytes, which leads to cytolysis via antibody-dependent cellular cytotoxicity (ADCC) and/or complement-mediated lysis. Ublituximab targets a novel epitope of CD20 that is not bound by ocrelizumab or ofatumumab (b) (4) , and, therefore, result in greater ADCC than ocrelizumab.[1]

BRIUMVI is administered by intravenous infusion with an initial infusion of 150 mg, a second infusion of 450 mg two weeks after the first dose, and subsequent infusions of 450 mg every 6 months. Ublituximab is a protein for which the expected metabolic pathway is degradation to small peptides and amino acids by ubiquitous proteolytic enzymes. The estimated mean terminal half-life is 22 days.[2]

The Biologics License Application (BLA) submission included data from adults with relapsing forms of multiple sclerosis enrolled in two Phase 3, randomized, multicenter, double-blind, double-dummy, active-controlled studies of ublituximab versus bioequivalent teriflunomide, two open-label, single-arm extension studies, and one placebo-controlled, multicenter, dose-finding, sequential study. The safety signals associated with ublituximab treatment were consistent with those observed with other anti-CD20 therapies, including infusion related reactions, infections, cytopenias, and reduction in immunoglobulins, particularly IgM. Opportunistic infections and reduction in IgG were not observed; however, longer-term experience is needed to fully assess these risks.[3] The proposed labeling (as of December 14, 2022) includes Warnings and Precautions for infusion reactions, infections, reduction in immunoglobulins, and fetal risk.[4]

[1] BRIUMVI (ublituximab). Draft clinical review dated November 13, 2022. Division of Neurology 2. U.S. Food and Drug Administration
[2] Proposed BRIUMVI labeling dated December 14, 2022
[3] See footnote 1
[4] See footnote 2

**1.2. Describe the Safety Concern**

The Division of Neurology 2 (DN2) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of ublituximab during pregnancy. Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2–4% (Centers for Disease and Prevention 2008, Food and Drug Administration 2014). Multiple sclerosis is a chronic inflammatory disease of the central nervous system leading to demyelination and neurodegeneration. The vast majority of patients initially follow a relapsing-remitting course, defined by acute exacerbations from which they typically completely or incompletely recover, with periods of relative clinical stability in between (Katz Sand 2015). Multiple sclerosis is commonly diagnosed in women of childbearing age and its incidence is two to three times higher in women than men. Women with multiple sclerosis are not less fertile and do not have more difficulty in completing a pregnancy to term compared with healthy controls (Voskuhl and Momtazee 2017). While evidence regarding the effect of multiple sclerosis on pregnancy is not entirely consistent, available data suggest that maternal multiple sclerosis may be associated with an increased rate of caesarean delivery and lower infant birth weights compared with women without multiple sclerosis (Kelly, Nelson et al. 2009).

Data on pregnancy exposure during clinical trials are insufficient to inform the risk of maternal, fetal, and infant outcomes associated with the use of ublituximab. The pivotal phase 3 clinical trials required contraception throughout the treatment period and for 20 weeks after cessation of active treatment and pregnancy tests every four weeks during the treatment and follow-up periods. The supportive Phase 2 study required contraception during the treatment period and 30 days after the last dose of study drug and pregnancy testing at screening, Day 15, and Week 24. One open-label extension study required contraception throughout the treatment period and for 20 weeks after cessation of active treatment and pregnancy tests at screening, week 3, week 24, and then every 24 weeks; the other open-label extension study required contraception throughout the treatment period and for 16 weeks after cessation of active treatment and pregnancy testing every 24 weeks. Among the nine subjects who became pregnant while on ublituximab, four resulted in healthy, full-term infants, three resulted in elective abortions, and two had unknown outcomes due to withdrawal of consent (one with conception following treatment completion). One subject who underwent elective abortion did so due to ectopic pregnancy, which required surgical intervention that was complicated by salpingitis and maternal death. The other two subjects with elective abortions did not have recorded any reasons triggering the decision. Among the three partner pregnancies in subjects on ublituximab, one resulted in a healthy, full-term infant, one resulted in elective abortion, and one had an unknown outcome due to withdrawal of consent.[5]

The potential for adverse effects of ublituximab on embryofetal and postnatal development was evaluated in an enhanced pre- and postnatal development (ePPND) study. Because ublituximab is not pharmacologically active in rodents, the study was conducted in separate groups of 16 pregnant cynomolgus monkeys that received weekly IV injections of ublituximab at doses of 0 or 30 mg/kg during the first, second, or third trimester of pregnancy. Due to the development of significant immune-mediated toxicities, dosing was terminated early. Only the subgroup dosed during the first trimester received all seven doses. Immune-mediated toxicity resulted in

[5] See footnote 1

a high rate of unscheduled maternal, fetal, and infant deaths. Seven offspring from the females dosed during the first trimester and one infant from females dosed during the second trimester survived the full 6-month postnatal period. The surviving offspring showed no adverse effects on embryofetal or postnatal development. However, two of the four infants born to females dosed during the second trimester showed significant abnormal findings: contractures and abnormal flexion of multiple limbs and tail, lack of grasp reflex, shortened mandible, elongated calvarium, enlarged ears, and muscle atrophy. Macroscopic findings noted were deepened sulci and narrow gyri in the brain, bilateral cerebral ventricular enlargement (correlated with degeneration/necrosis, graded moderate). These findings were considered related to ublituximab. The fourth infant was euthanized due to premature delivery. Because a single dose level was administered in this study, no NOAEL (no observed adverse effect level) was identified. [6]

The current proposed labeling, as of December 14, 2022, includes warnings and precautions for fetal risk.[7] It states *"Based on data from animal studies, BRIUMVI may cause fetal harm when administered to a pregnant woman. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception during BRIUMVI treatment and for 6 months after the last dose."*

Section 8.1 (Pregnancy) states:

*"Risk summary*
*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 ublituximab-xiiy, monoclonal antibodies can be actively transported across the placenta, and BRIUMVI may cause immunosuppression in the in-utero exposed infant [see Clinical Considerations, Warnings and Precautions (5.2, 5.3), and Clinical Pharmacology (12.1), (12.2)].*
*Weekly intravenous administration of ublituximab-xiiy to pregnant monkeys during the first, second, or third trimester of pregnancy* (b) (4) *resulted in embryofetal loss; administration during the second trimester resulted in external, skeletal, and visceral abnormalities in* (b) (4) *(see Data).*
*The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.*

*Clinical Considerations*
*Fetal/Neonatal adverse reactions*
*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*

[6] BRIUMVI (ublituximab). Draft non-clinical review dated November 29, 2022. Division of Neurology 2. U.S. Food and Drug Administration
[7] See footnote 2

*antibodies during pregnancy. Avoid administering live vaccines to neonates and infants exposed to BRIUMVI in utero until B-cell recovery occurs [see Warnings and Precautions (5.2), and Clinical Pharmacology (12.2)].*

*Data*
*Animal Data*
*Weekly intravenous administration of ublituximab-xiiy (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 and death and embryofetal loss. Dosing was terminated in dams after only two doses during the third trimester because of multiple deaths in dams dosed during the first and second trimesters.*
*Ublituximab-related external, viscera, and skeletal abnormalities occurred in two* (b) (4) *from dams exposed during the second trimester of pregnancy. Histopathology evaluations revealed minimal to moderate degeneration/necrosis in the brain.* (b) (4) *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.* (b) (4) *abnormalities were absent in dams exposed during the first trimester of pregnancy.*
(b) (4)

Section 8.3 (Females and Males of Reproductive Potential) states:

*"Contraception*
*Females*
*Females of reproductive potential should use effective contraception while receiving BRIUMVI and for 6 months after the last dose of BRIUMVI."*

### 1.3. FDAAA Purpose (per Section 505(o)(3)(B))

*- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS*

| *Purpose (place an "X" in the appropriate boxes; more than one may be chosen)* | |
|---|---|
| Assess a known serious risk | |
| Assess signals of serious risk | |
| Identify unexpected serious risk when available data indicate potential for serious risk | X |

## 2. REVIEW QUESTIONS

### 2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of child bearing age is a general concern

### 2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

### 2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☒ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☒ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: Alternative study designs would be considered: e.g., retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study.

### 2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☒ Covariates
☒ Analytical Tools

*For any checked boxes above, please describe briefly:*

Outcomes: ARIA lacks access to medical records. The pregnancy registry being considered requires that an expert clinical geneticist or dysmorphologist review and classify medical records of all major congenital malformations. Also, although in a first stage, the study using claims or electronic medical data may be algorithm-based, if it shows an imbalance in any of the outcomes being investigated, FDA will require outcome validation in the selected database(s) or a chart-confirmed analysis.

Covariates: ARIA does not have detailed information on potential confounders. The prospective pregnancy registry being considered should be able to include information on potential covariates, such as lifestyle factors, maternal education and socio-economic conditions, over-the-counter prenatal supplements, and disease phenotype, activity, and progression.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully tested and implemented in postmarketing surveillance of maternal and fetal outcomes. The ARIA analytic tools that assess drug use in pregnancy (and maternal and neonatal outcomes) currently include only women with a live-birth delivery.

**2.5. Please include the proposed PMR language in the approval letter.**

The following language has been proposed by DN2, as of December 14, 2022, for the PMRs related to pregnancy outcomes:

*PMR 4337-2: Prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to BRIUMVI (ublituximab) during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to BRIUMVI (ublituximab) before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.*

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|---|---|
| *Draft Protocol Submission:* | *07/2023* |
| *Final Protocol Submission:* | *03/2024* |
| *Annual Interim Report Submissions:* | *03/2025—03/2034* |
| *Study Completion:* | *03/2035* |
| *Final Report Submission:* | *03/2036* |

*PMR 4337-3: A pregnancy outcomes study using a different study design than provided for in PMR 4337-2 (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess pregnancy complications, major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Briumvi (ublituximab-xiiy) during pregnancy compared to an unexposed control population.*

| | |
|---|---|
| *Draft Protocol Submission:* | *07/2023* |
| *Final Protocol Submission:* | *03/2024* |
| *Annual Interim Report Submissions:* | *03/2025—03/2034* |
| *Study Completion:* | *03/2035* |
| *Final Report Submission:* | *03/2036* |

**REFERENCES**

Centers for Disease, C. and Prevention (2008). "Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005." MMWR Morb Mortal Wkly Rep **57**(1): 1-5.

Food and Drug Administration. (2014). "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format. Draft Guidance." Guidance for Industry Retrieved February 3, 2020, from

Katz Sand, I. (2015). "Classification, diagnosis, and differential diagnosis of multiple sclerosis." Curr Opin Neurol **28**(3): 193-205.

Kelly, V. M., L. M. Nelson and E. F. Chakravarty (2009). "Obstetric outcomes in women with multiple sclerosis and epilepsy." Neurology **73**(22): 1831-1836.

Voskuhl, R. and C. Momtazee (2017). "Pregnancy: Effect on Multiple Sclerosis, Treatment Considerations, and Breastfeeding." Neurotherapeutics **14**(4): 974-984.

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12/15/2022 07:59:20 AM

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PATRICIA L BRIGHT
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**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

# Memorandum

**Date:** 11/18/2022

**To:** Laura Baldassari Clinical Reviewer, M.D.
Division of Neurology Products (DN II)

Rania Younes, Regulatory Project Manager, (DN II)

Tracy Peter, Associate Director for Labeling, (DN I/II)

**From:** Samuel Fasanmi, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Aline Moukhtara, RN, MPH, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for Briumvi (ublituximab-xiiy) injection, for intravenous use

**BLA**: 761238

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In response to DN II consult request dated October 26, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original BLA submission for Briumvi (ublituximab-xiiy) injection, for intravenous use.

**Labeling**: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN II on November 07, 2022, and are provided below.

**Medication Guide**: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on November 16, 2022.

**Carton and Container Labeling**: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 16, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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SAMUEL A FASANMI
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**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Medical Policy**

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | November 16, 2022 |
| To: | Rania Younes, PharmD<br>Regulatory Project Manager<br>**Division of Neurology II (DN2)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)**<br><br>Marcia Williams, PhD<br>Team Leader, Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Mary Carroll, BSN, RN<br>Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>Samuel Fasanmi, PharmD<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Medication Guide (MG) |
| Drug Name (established name): | BRIUMVI (ublituximab-xiiy) |
| Dosage Form and Route: | injection, for intravenous use |
| Application Type/Number: | BLA 761238 |
| Applicant: | TG Therapeutics, Inc |

## 1 INTRODUCTION

On September 24, 2021, TG Therapeutics, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761238 BRIUMVI (ublituximab-xiiy) injection, for intravenous use. The purpose of the application is to seek approval for the use of BRIUMVI (ublituximab-xiiy) injection for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II (DN2) on October 29, 2021 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BRIUMVI (ublituximab-xiiy) injection, for intravenous use.

## 2 MATERIAL REVIEWED

- Draft BRIUMVI (ublituximab-xiiy) MG received on September 24, 2021, and received by DMPP and OPDP on November 7, 2022.
- Draft BRIUMVI (ublituximab-xiiy) Prescribing Information (PI) received on September 24, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 7, 2022.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8$^{th}$ grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the MG is consistent with the approved comparator labeling where applicable.

## 4 CONCLUSIONS

The MG is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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MARY E CARROLL
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MARCIA B WILLIAMS
11/16/2022 02:32:00 PM

LASHAWN M GRIFFITHS
11/16/2022 06:24:02 PM

# MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| Date of This Memorandum: | September 23, 2022 |
| Requesting Office or Division: | Division of Neurology 2 (DN 2) |
| Application Type and Number: | BLA 761238 |
| Product Name and Strength: | Briumvi (ublituximab-xiiy) injection, 150 mg/6 mL (25 mg/mL) |
| Applicant/Sponsor Name: | TG Therapeutics, Inc. |
| OSE RCM #: | 2021-1941-2 |
| DMEPA 2 Safety Evaluator: | Beverly Weitzman, PharmD |
| DMEPA 2 Acting Team Leader: | Stephanie DeGraw, PharmD |

## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on September 16, 2022 for Briumvi. The Division of Neurology 2 (DN 2) requested that we review the revised container label and carton labeling for Briumvi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review memorandum.[a]

## 2 CONCLUSION AND RECOMMENDATIONS

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Weitzman, B. Label and Labeling Review Memo for Briumvi (BLA 761238). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 AUG 29. RCM No.: 2021-1941-1.

## APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 16, 2022

### Container label


### Carton labeling

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BEVERLY WEITZMAN
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STEPHANIE L DEGRAW
09/23/2022 09:48:51 AM

**Division of Hepatology and Nutrition Consultation**

**Drug-induced Liver Injury Team**

| | |
|---|---|
| **NDA** | 761238 |
| **Consultation Issue** | Drug-induced liver injury (DILI) |
| **Drug Product** | Ublituximab |
| **Indication** | Multiple sclerosis |
| **Applicant** | TG Therapeutics |
| **Requesting Division** | Division of Neurology 2 |
| **Primary Reviewer** | Ling Lan, MD, PhD, Clinical Analyst, DILI Team, DHN |
| **Secondary Reviewer** | Paul H. Hayashi, MD, MPH<br>DILI Team Lead, OND/DHN |
| **Reviewer**<br>**Office of Pharmacoepidemiology** | Mark Avigan, MD, CM<br>Associate Director, OPE/OSE |
| **Signatory Authority** | Frank Anania, MD<br>Deputy Director, OND/DHN |
| **Assessment Date** | Sep 6, 2022 |

**Context:** Ublituximab (UBX) is a recombinant, chimeric IgG1 monoclonal antibody that binds CD20 on B-lymphocytes leading to their destruction and decline in serum antibody production. It is given intravenously for the treatment of multiple sclerosis (MS) in this BLA. Decline in antibody production leads to less immune complex deposition that is part of the pathophysiology of MS. The Division of Neurology 2 (DN2) noted a subject with liver test elevations meeting Hy's Law criteria in the pivotal phase III studies. Frequency of liver enzyme elevations were similar between the UBX and teriflunomide (TFL) comparator arms, but DN2 raised concerns that elevations were equal to a drug with a boxed warning for liver injury (TFL). DN2 requested the DILI Team's causality assessment of the subject meeting liver biochemistry criteria for Hy's Law and opinion on direct hepatotoxicity risk (i.e., non-hepatitis B reactivation risk).

**Executive Summary:** We do not see a liver injury risk that would hold up approval for this BLA. The subject with serum liver tests meeting Hy's Law criteria had acute hepatitis C and not DILI. One other subject had hepatocellular jaundice due to "chronic hepatitis B" according to the sponsor. Latencies for this subject were consistent with hepatitis B reactivation and not DILI. There was no significant imbalance in liver enzyme elevations between UBX and teriflunomide (TFL) treatment arms. We acknowledge that TFL carries a boxed warning for hepatotoxicity, but unlike TFL, there are no cases of significant DILI in UBX's pivotal trials or DILI risk for UBX's class of drug. TFL's related compound, leflunomide has a well-known direct hepatotoxicity risk, while anti-CD20 agents do not. Nevertheless, the one case of liver injury due to hepatitis B reinforces the need to label for hepatitis B reactivation risk with UBX. Full assessment and recommendations are in Section 5.0.

**Consultation Sections:**

**Section 1.0** – Target Disease and Rationale
**Section 2.0** - ADME pertinent to DILI
**Section 3.0** - Non-clinical data pertinent to DILI.
**Section 4.0** - Clinical data
**Section 5.0** – Assessment & Recommendations.

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Abbreviations:
ADA: anti-drug antibodies
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AP: alkaline phosphatase
AST: aspartate aminotransferase
AT: aminotransferase (ALT and/or AST)
BMI: body mass index
CPK: creatinine phosphokinase
CT: computerized tomography
CYP: cytochrome P450
DB: direct bilirubin
DILI: drug-induced liver injury
GGT: gamma-glutamyl transferase
HBV: hepatitis B virus
HCV: hepatitis C virus
HDS: herbal and dietary supplements
IP: investigational product
MRI: magnetic resonance imaging
MS: multiple sclerosis
R-value: ALT/ULN ÷ ALP/ULN
TB: total bilirubin
TFL: teriflunomide
RRMS: relapsing-remitting multiple sclerosis
US: ultrasound
UBX: Ublituximab
ULN: upper limit of normal

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1.0 Target Disease and Rationale

1.1 Disease: Multiple sclerosis (MS) is an inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS) that affects approximately 2.8 million people worldwide and the prevalence is rising.[1] Multiple sclerosis represents the leading cause of non-traumatic neurologic disability in young and middle-aged adults.[2] Common symptoms and signs include sensory loss in the limbs, visual loss, motor loss, and gait

[1] Walton C, et al. Mult Scler 2020
[2] Olek MJ, at al. UpToDate, Mar 16, 2022 (Accessed April 26, 2022)

disturbance. The clinical course of MS typically manifests as relapsing-remitting multiple sclerosis (RRMS), characterized by initial episodes of transient neurological compromise (synonymously called relapses, clinical exacerbations, or attacks) with variable recovery (remission), eventually leading to cumulative deficits that may increase acutely with each relapse. In progressive MS, which includes primary and secondary progressive MS (PPMS and SPMS, respectively), cumulative deficits may increase gradually independent of, or in the absence of, relapses.

Current treatment aims to control acute relapses primarily, and include corticosteroids, adrenocorticosteroid hormone, teriflunomide (TFL), plasmapheresis and immunoadsorption. Steroid-based therapies have proven efficacy but have multiple side-effects. None of the therapies for acute relapses have shown benefit in preventing long-term disability or reducing future attacks.[3] Disability can be significant with 76% needing ambulatory aid after 45 years of disease.[4]

1.2 Rationale: Autoantibodies are thought to be part of the pathophysiology of MS by forming immune complexes that lead to proinflammatory cytokine and chemokine production. This inflammatory response is hypothesized to contribute to the neuronal demyelination of MS. Ublituximab (UBX) is a recombinant, IgG1 chimeric, monoclonal antibody directed against CD20, a transmembrane antigen on B-lymphocytes. Engaging this antigen with monoclonal antibodies leads to B-cell lysis and significant decline in serum antibodies. Ocrelizumab, an anti-CD20 humanized monoclonal is approved for the treatment of relapsing MS. Presumably UBX will act by a similar mechanism as ocrelizumab.

2.0 ADME data pertinent to DILI

2.1 Absorption: GI absorption not pertinent due IV administration of this monoclonal antibody

2.2 Distribution: Volume of distribution in monkeys ranged from 45 to 105 ml/kg, or twice the monkey plasma volume.

2.3 Metabolism: As a monoclonal antibody, UBX is expected to be degraded peripherally into small peptides and amino acids via catabolic pathways in a manner like endogenous IgG. Liver metabolism and metabolites are predicted to be insignificant, though the possibility for small peptides forming neoantigens leading to DILI via immune-mediated mechanisms is a theoretical possibility.

2.4 Excretion: No biliary or renal excretion is expected for this monoclonal antibody. Systemic clearance is 0.5 to 4 mL/hr/kg which is estimated to be less than 1% of liver blood flow in monkeys.

3.0 Non-clinical data

[3] Olek MJ et al. UpToDate, Jan 10, 2022 (Accessed April 26, 2022)
[4] Kister I, et al. Neurology, 2013

3.1 In vitro data: Traditional in vitro studies (e.g., microsome, glutathione trapping, transporter inhibition) are not reported and not pertinent to this monoclonal antibody metabolism or its potential for toxicity.

3.2 Animal data: Toxicity was tested in cynomolgus monkeys and rabbits in single and repeat dosing experiments. Toxicity studies included immune-mediated injury associated with anti-drug antibodies (ADA). Formation of ADAs was common in the longer-term exposure (9 of 10 monkeys at 26 weeks of dosing). Liver histopathology results were noted at the NOAEL of 30mg/kg in one female monkey and in several male and female monkeys at 50 mg/kg. However, the liver injury observed was typically in the context of overall intolerance and overall poor clinical condition, decreased oral intake, and multi-organ histopathologic changes.

4.0 Clinical data:

4.1 Approved agents pertinent to this BLA:

4.1.1 Approved anti-CD20 monoclonal antibodies and teriflunomide (comparator agent) are shown in **Table 1**.

**Table 1**: Approved anti-CD20 agents and TFL

| Agent (Year approved) | Labeling for liver injury | LiverTox®[5] | Indication(s) |
|---|---|---|---|
| Anti-CD20 monoclonals | | | |
| Rituximab (1997) | Warnings/Precautions: Hepatitis B reactivation | 10-15% TA elevations<br>Rare severe injury<br>HBV reactivation<br>Likelihood score A (for HBV issue mainly) | Non-Hodgkin's lymphoma (NHL); chronic lymphocytic leukemia (CLL); rheumatoid arthritis (RA) |
| Ibritumomab (2002) | None (given for 9 days only) | NA | NHL; follicular lymphoma |
| Ofatumumab (2009) | Warnings/Precautions: Hepatitis B reactivation | "uncommon" TA elevations<br>HBV reactivation<br>Likelihood score: E* | CLL |
| Obinutuzumab (2013) | Boxed warning: Hepatitis B reactivation | NA | CLL; follicular lymphoma |
| Ocrelizumab (2017) | Contraindications: Acute hepatitis B<br>Dosage & Administration: HBV screening | 1-2% TA elevation<br>HBV reactivation<br>Likelihood score: D | Relapsing or primary progressive MS |
| Comparator agent (teriflunomide): small molecule, pyrimidine synthesis inhibitor | | | |
| Teriflunomide (2012) | Boxed warning: Hepatotoxicity | ALT elevations 13-15% vs. 9% PBO<br>Discontinuance in 2-3%<br>Rare severe injury usually in first 6 mo. | Relapsing MS |

NA = not available

In general, the anti-CD20 monoclonal antibodies rarely cause a "direct" DILI, but rather indirect injury by reactivation of quiescent hepatitis B virus (HBV) infection. However,

[5] LiverTox® https://www.ncbi.nlm.nih.gov/books/NBK547852/

HBV reactivation can be severe leading to fatalities and need for liver transplantation. Guidelines and expert opinion suggest use of prophylaxis with oral anti-HBV agents while patients are being treated with anti-CD20 monoclonal antibodies, and for several months afterwards.[6],[7]

DHN includes excerpts from the TFL label[8] due to concerns for similar enzyme elevations in the UBX treatment and TFL comparator arms in this BLA. The boxed warning for TFL liver injury is due to TFL's similarity to leflunomide and a possible severe injury case in the pivotal trials.

Boxed warning:

*Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide, which is indicated for rheumatoid arthritis. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide. Concomitant use of AUBAGIO with other potentially hepatotoxic drugs may increase the risk of severe liver injury. Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for six months after starting AUBAGIO [see Warnings and Precautions (5.1)]. If drug induced liver injury is suspected, discontinue AUBAGIO and start an accelerated elimination procedure with cholestyramine or charcoal [see Warnings and Precautions (5.3)]. AUBAGIO is contraindicated in patients with severe hepatic impairment [see Contraindications (4.1)]. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO.*

Section 5.1:

*In placebo-controlled trials, ALT greater than three times the ULN occurred in 14/429 (3%) and 21/415 (5%) of patients on teriflunomide 7 mg and 14 mg, respectively, and 17/421 (4%) of patients on placebo, during the treatment period. These elevations occurred mostly within the first year of treatment. Half of the cases returned to normal without drug discontinuation. In clinical trials, if ALT elevation was greater than three times the ULN on two consecutive tests, AUBAGIO was discontinued, and patients underwent an accelerated elimination procedure [see Warnings and Precautions (5.3)]. Of the patients who underwent discontinuation and accelerated elimination in controlled trials, half returned to normal or near normal values within 2 months. One patient in the controlled trials developed ALT 32 times the ULN and jaundice 5 months after initiation of AUBAGIO 14 mg treatment. The patient was hospitalized for 5 weeks and recovered after plasmapheresis*

[6] Loomba R, Liang JT. Gastroenterology, 2017
[7] Reddy KR, et al. Gastroenterology, 2015
[8] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202992s000lbl

*and cholestyramine accelerated elimination procedure. Teriflunomide-induced liver injury in this patient could not be ruled out.*

4.2 Study protocol(s):

4.2.1 Clinical studies included in the Integrated Summary of Safety (ISS): The ISS consisted primarily of two pivotal phase 3 studies as well as a phase 3 trial that has an ongoing open label extension (OLE), two phase 2 studies with one ongoing OLE phase 2 trial. For the purposes of this consult DHN focused on the two non-OLE phase 3 studies. These two studies were identical in design and exposed 545 MS subjects to UBX. (**Table 2**)

**Table 2:**

**List of Clinical Studies in RMS Included in the BLA**

| **Study ID/ Phase (Status)/ Number of Sites (Countries)/ NCT Number** | **Study Design** | **Drug Product(s)/ Route of Administration/ Dose/Infusion time** | **Number of Subjects Treated** |
|---|---|---|---|
| TG1101-RMS301 (ULTIMATE I)/ Phase III (completed)/ 57 (USA [12], Spain [3], Poland [5], Serbia [4], Georgia [7], Russia [11], Belarus [4], United Kingdom [1], and Ukraine [10])/ NCT03277261 | Randomized, multicenter, double-blinded, double-dummy, active-controlled study to assess the efficacy, safety, and tolerability of ublituximab/oral placebo as compared to teriflunomide/IV placebo in subjects with RMS | Ublituximab/placebo oral: Ublituximab IV W1 D1: 150 mg/4 h; W3 D15, W24, W48, W72: 450 mg/1 h<br>Placebo PO QD on W1 to W95<br><br>Teriflunomide/placebo IV: Teriflunomide PO W1 D1 to W95 last day: 14 mg QD<br>Placebo IV W1 D1, W3 D15, W24, W48, and W72 | Total: 548<br><br>Ublituximab: 273<br>Teriflunomide: 275 |
| TG1101-RMS302 (ULTIMATE II)/ Phase III (completed)/ 47 (USA [10], United Kingdom [2], Spain [3], Poland [5], Croatia [3], Russia [11], Belarus [3], and Ukraine [10])/ NCT03277248 | Randomized, multicenter, double-blinded, double-dummy, active-controlled study to assess the efficacy, safety, and tolerability of ublituximab/oral placebo as compared to teriflunomide/IV placebo in subjects with RMS | Ublituximab/placebo oral: Ublituximab IV W1 D1: 150 mg/4 h; W3 D15, W24, W48, W72: 450 mg/1 h<br>Placebo PO QD on W1 to W95<br><br>Teriflunomide/placebo IV: Teriflunomide PO W1 D1 to W95 last day: 14 mg QD<br>Placebo IV W1 D1, W3 D15, W24, W48, and W72 | Total: 545<br><br>Ublituximab: 272<br>Teriflunomide: 273 |
| TG1101-RMS303/ Phase III (ongoing)/ 90 (USA [18], Poland [9], Croatia [3], Serbia [4], Georgia [7], Russia [22], Belarus [7], and Ukraine [20])/ NCT04130997 | Open-label, single-arm, extension study of TG1101-RMS301 and TG1101-RMS302 | Ublituximab IV W1 D1: 150 mg/4 h; W3 D15, W24, W48, W72, W96, W120, W144, and W168: 450 mg/1 h | Total: 642[a] |

| | | | |
|---|---|---|---|
| TG1101-RMS201/<br>Phase IIa (completed)/<br>9 (USA)/<br>NCT02738775 | Placebo-controlled, multicenter, dose-finding study in subjects with RMS | Ublituximab IV<br>D1, D15, and W24<br>Cohort 1: 150 mg/4 h, 450 mg/3 h, 450 mg/1.5 h<br>Cohort 2: 150 mg/4 h, 450 mg/1.5 h, 450 mg/1 h<br>Cohort 3: 150 mg/4 h, 450 mg/1 h, 600 mg/1 h<br>Cohort 4: 150 mg/3 h, 600 mg/1 h, 600 mg/1 h<br>Cohort 5: 150 mg/2 h, 600 mg/1 h, 600 mg/1 h<br>Cohort 6: 150 mg/1 h, 600 mg/1 h, 600 mg/1 h<br>or<br>Placebo IV[b]<br>D1 and D15 | Total: 49<br><br>Ublituximab: 36<br>Placebo: 13<br>(12 subjects received ublituximab after D28) |
| TG1101-RMS201E/<br>Phase II (ongoing)/<br>8 (USA)/<br>NCT03381170 | Open-label, extension study of TG1101-RMS201 | Ublituximab IV<br>450 mg/1 h every 24 weeks for up to 192 weeks | Total: 43[c] |

***Source: ?***

4.2.2 Phase 3 studies: TG1101-RMS301 (*UbLiTuximab in Multiple Sclerosis Treatment Effects,* ULTIMATE I) and TG1101-RMS302 (*UbLiTuximab in Multiple Sclerosis Treatment Effects*, ULTIMATE II) were identical in design (**Table 3** & **Figure 1**). The studies were double dummy blinded with subjects randomized 1:1 to IV UBX + oral PBO or IV PBO + oral TFL. Four UBX doses were given between Day 1 and week 48, while the oral agent (PBO or TFL) continued to week 96.

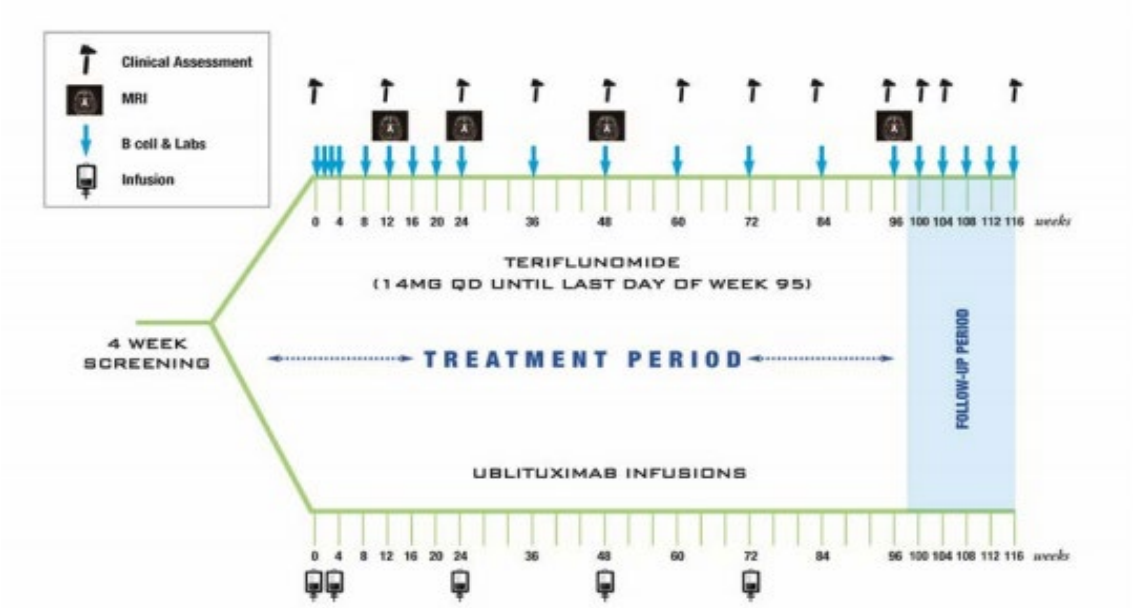
**Table 3: Summary of phase III studies' design**

**Phase III**

**: Ublituximab/oral placebo and Teriflunomide (14 mg)/IV placebo**

| | Week 1 Day 1 | Week 3 Day 15 | Week 24 | Week 48 | Week 72 | Week 96 |
|---|---|---|---|---|---|---|
| **Ublituximab plus oral placebo** | UTX (150 mg/ 4h) | UTX (450 mg/ 1h) | UTX (450 mg/1h) | UTX (450 mg/ 1h) | UTX (450 mg/ 1h) | |
| | Oral Placebo QD* from Week 1 Day 1 until last day of Week 95 | | | | | |
| **Teriflunomide plus placebo infusion** | Teriflunomide (14 mg) QD* from Week 1 Day 1 until last day of Week 95 | | | | | |
| | Infusion Placebo | Infusion Placebo | Infusion Placebo | Infusion Placebo | Infusion Placebo | |

**Figure 1: Schematic of phase 3 studies' design and schedule of events**




4.2.3 Inclusion and exclusion criteria pertinent to DILI

4.2.3.1 Inclusion criteria:

a) Age 18 to 55 years

4.2.3.2 Exclusion criteria:

a) "Known history of active HBV or HCV", not otherwise specified (NOS). The DILI team found no data regarding anti-HBc, HBsAg, HBV DNA, HCV RNA, HCV therapy or HBV therapy criteria (past, or current), or evidence that subjects were placed on HBV therapy for prophylaxis.
b) "Clinically significant chronic liver or biliary disease"
c) Moderate to severe hepatic impairment (Child Pugh B or C)
d) ALT >2x ULN
e) AST >2x ULN
f) Platelet count <150,000 /mm$^3$
g) Symptomatic or history of congestive heart failure (NY Heart Association III-IV)

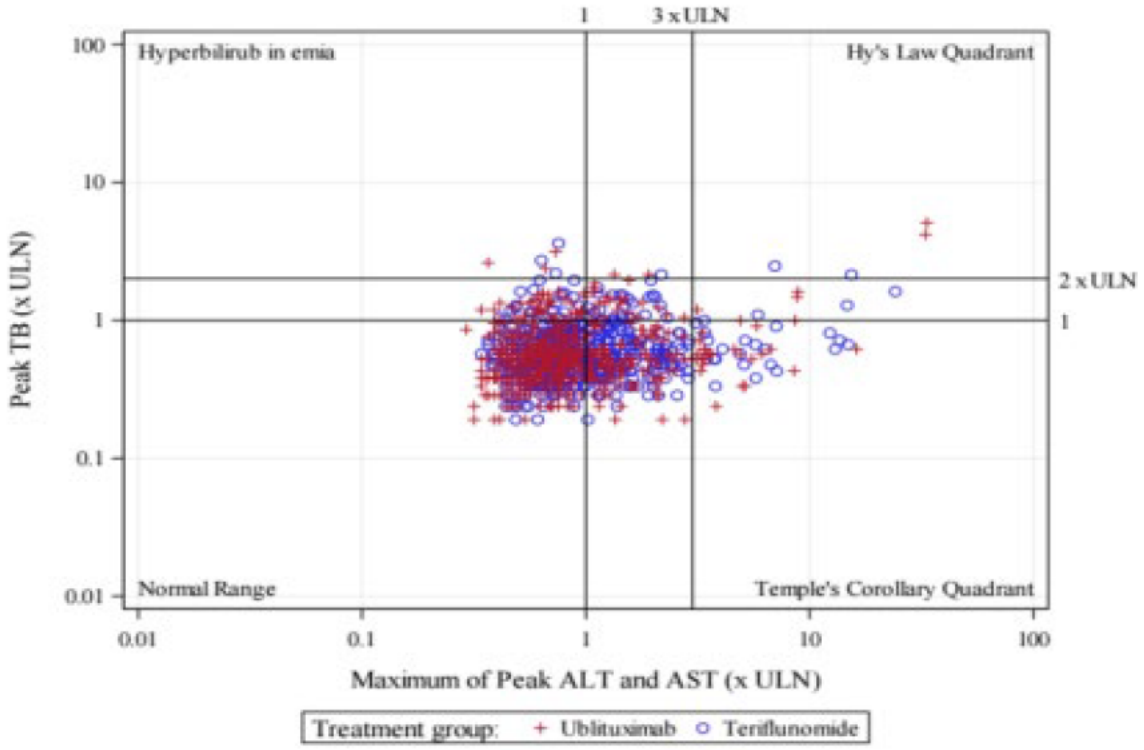
4.3 eDISH, summary liver enzyme tables, liver related TEAE, SAEs.

4.3.1 eDISH hepatocellular scatterplot (Figure 2)[9]: There were four subjects in the Hy's Law quadrant, two from the UBX arm and two from the comparator arm. Excluding the two subjects randomized to UBX in the Hy's Law quadrant, there appeared to be a greater shift in transaminase to the right (more elevated) for the TFL arm.

[9] BLA761238 (761238 - 0042 - (42) - 2022-08-12 - ORIG-1 /Clinical/Response To Information Request) - Summary of Clinical Safety (#74)

**Figure 2:** eDISH for pooled phase III studies

**Figure 2: Liver Function Abnormalities Peak Values of ALT or AST and TBL in the Pooled Pivotal Phase III Studies (Safety Population)**




4.3.2 Elevations in liver tests between groups from the pooled pivotal phase 3 studies. (**Table 4**). ALT ≥5x ULN occurred slightly more often in the TFL arm while AST ≥5x ULN occurred slightly more often in the UBX arm. These differences tended to continue at higher ALT and AST cut-offs (i.e., ≥8x ULN, ≥10x ULN).

**Table 4:** Number and percentages of subjects with peaks liver test elevations at varying multiples of ULN and by study arm for two pooled phase 3 studies.

| Criteria | UBX (N = 545) n (%) | TFL (N = 548) n (%) |
|---|---|---|
| ALT | | |
| ≥3x ULN | 21 (3.9) | 24 (4.4) |
| ≥5x ULN | 9 (1.7) | 13 (2.4) |
| ≥8x ULN | 6 (1.1) | 6 (1.1) |
| ≥10x ULN | 3 (0.5) | 6 (1.1) |
| >20x ULN | 1 (0.2) | 1 (0.2) |
| AST | | |
| ≥3x ULN | 24 (4.4) | 16 (2.9) |
| ≥5x ULN | 12 (2.2) | 10 (1.8) |
| ≥8x ULN | 4 (0.7) | 2 (0.4) |
| ≥10x ULN | 2 (0.4) | 2 (0.4) |
| >20x ULN | 2 (0.4) | 1 (0.2) |

| | | |
|---|---|---|
| AP | | |
| ≥2x ULN | 0 (0) | 3 (0.5) |
| TB | | |
| ≥2x ULN | 7 (1.3) | 6 (1.1) |

4.4 Case level analysis

4.4.1 Summary of cases: DHN assessed 15 subjects (2.7% of UBX exposed subjects) with significant elevation in liver tests (e.g., ALT or AST >5x ULN +/- TB >2x ULN), including the two subjects who received UBX and had AT and TB elevations consistent with Hy's Law. (**Table 5**) Neither of these two Hy's Law (highlighted in blue in **Table 5)** were due to DILI. Thus, there were no Hy's Law cases associated with UBX in this BLA.

Two subjects had possible DILI with short latencies from initiating the biologic (27 days), but the AT elevations resolved quickly with continued exposure to UBX without intervention or treatment. If DILI occurred, clinical relevance is low due to rapid tolerance (AT normalization in 7-28 days) without elevation in TB. DHN considered the remaining 11 of 15 subjects as unlikely DILI due to UBX. Overall, the alternate diagnoses for the possible and unlikely cases are Gilbert's Syndrome (5); acetaminophen injury (1); hepatitis B (1), acute hepatitis C (1); pneumonia (1); and unknown (6). All the cases labeled as unknown had latencies too short or too long following UBX start or stop, respectively to diagnose UBX hepatotoxicity.

**Table 5: Demographics, DILI assessments and serum liver tests for fifteen subjects with significant liver tests abnormalities in the phase 3 pivotal trials.**

| # | ID | Causality Score^ | Alternate diagnosis | Study | Age (yr) | Sex | Race | Hy's Law | Latency from start drug (da)* | Latency from stop drug (da)~ | ALT peak (U/L) | AST peak (U/L) | ALP peak (U/L) | Bilirubin peak (mg/dL) | Predominant indirect bilirubin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | (b) (6) | 4 | Unknown. | TG1101-RMS301 | 45 | F | Unknown | No | 27 | -832 | 226 | 83 | 104 | 0.35 | NA |
| 2 | | 4 | Unknown | TG1101-RMS301 | 44 | M | Unknown | No | 27 | -637 | 731 | 334 | 104 | 0.18 | NA |
| 3 | | 5 | APAP | TG1101-RMS301 | 38 | F | White | No | 27 | -637 | 388 | 229 | 115 | 0.29 | NA |
| 4 | | 5 | Gilbert's | TG1101-RMS301 | 44 | F | Unknown | No | 169 | -495 | 34 | 34 | 104 | 3.86 | Yes |
| 5 | | 5 | Gilbert's | TG1101-RMS302 | 26 | M | Unknown | No | -98 | -770 | 34 | 34 | 104 | 3.16 | Yes |
| 6 | | 5 | Gilbert's | TG1101-RMS302 | 26 | M | Unknown | No | -23 | -687 | 34 | 34 | 104 | 2.92 | Yes |
| 7 | | 5 | Gilbert's | TG1101-RMS301 | 27 | F | Unknown | No | 0 | -665 | 34 | 34 | 104 | 2.63 | Yes |
| 8 | | 5 | Gilbert's | TG1101-RMS301 | 27 | M | Unknown | No | 14 | -650 | 34 | 34 | 104 | 3.22 | Yes |
| 9 | | 5 | Hepatitis B | TG1101-RMS302 | 46 | F | Unknown | No | 499 | 163 | 477 | 1371 | 179 | 6.26 | No |
| 10 | | 5 | Hepatitis C | TG1101-RMS301 | 44 | M | Unknown | No | 27 | 13 | 1485 | 1027 | 152 | 5.15 | No |
| 11 | | 5 | Pneumonia | TG1101-RMS301 | 30 | M | Unknown | No | 1 | -492 | 396 | 278 | 111 | 1.23 | NA |
| 12 | | 5 | Unknown | TG1101-RMS301 | 24 | M | White | No | 737 | 73 | 77 | 252 | 104 | 0.41 | NA |
| 13 | | 5 | Unknown | TG1101-RMS302 | 39 | F | Unknown | No | 1 | -505 | 240 | 238 | 104 | 0.41 | NA |
| 14 | | 5 | Unknown | TG1101-RMS302 | 27 | M | Unknown | No | 424 | -241 | 144 | 227 | 104 | 0.41 | NA |
| 15 | | 5 | Unknown. | TG1101-RMS301 | 24 | F | Unknown | No | 14 | -493 | 63 | 211 | 104 | 0.53 | NA |

^1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

*negative values indicate injury onset occurred *before* drug start by that many negative days (i.e., date of injury onset - date of drug start)

~negative values indicate the subject *remained on drug* for that many negative days after injury onset (i.e., date of injury onset - date of drug stop)

NA = not applicable

Blue font = cases that met liver biochemistry criteria for Hy's Law

4.4.2 Individual cases: DHN discusses in detail case findings for the two subjects who randomized to UBX and had liver biochemistries meeting Hy's Law criteria. DHN considers both as unlikely DILI from UBX.

4.4.2.1 Subject (b) (6) (Study TG1101-RMS301): Unlikely DILI due to UBX.

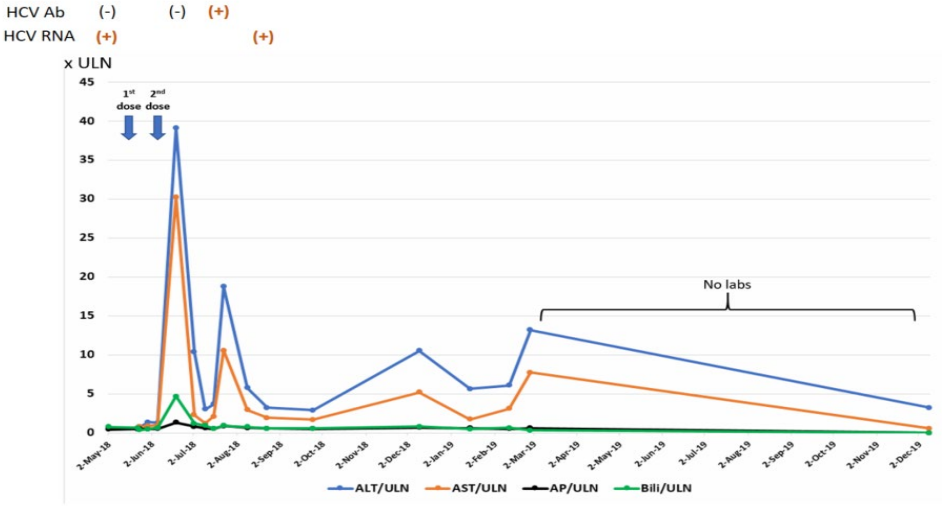
*Summary*: This is a 44-year-old man with MS since Oct 2017. He enrolled in Ukraine.

At baseline, he had no relevant medical history. BMI was 27.5 kg/m$^2$, and he denied any alcohol consumption or herbal or dietary supplements (HDS) use. He took no medications of concern for DILI. His ALT was 24 U/L, AST 18 U/L, AP 49 U/L and TB was normal at baseline.

The subject started UBX on (b) (6). On (b) (6), ALT was 1485, AST 1027, AP 152, TB 5.15 mg/dL. He reported yellow skin and eyes on (b) (6). US of the right upper quadrant was without evidence of cholelithiasis, dilated bile ducts, or hepatic masses. ANA was negative. IgG levels were 1.0 g/dL at Day 1 and Day 15. IgG levels fell to 0.95 g/dL on Day 93, and then increased to >1.8 g/dL thereafter. No other laboratory tests were provided. He had a negative HCV antibody test and a negative HBsAg at baseline, but anti-HBc status was not initially provided. Aminotransferases fluctuated for several months thereafter before falling to normal or near normal. (**Figure 3**) No therapeutic maneuvers were recorded for this injury. The subject's last UBX infusion was (b) (6) (13 days prior to the rise in serum aminotransferases) before UBX was permanently stopped. The subject exited the study on (b) (6).

DIA sent a query to the sponsor on (b) (6), regarding stored samples for additional diagnostic tests (e.g., viral serologies and nucleic acid tests [PCR]). Stored samples yielded negative HBV serologies. However, HCV RNA was detected, and the quantitative PCR revealed 21.1 M IU/ml with negative HCV antibody (Ab) at Day 1 (pre-dose). On (b) (6) (injury onset) HCV Ab was still negative, but anti-HCV antibody seroconversion was noted by (b) (6). HCV RNA was still positive at 23.6 M IU/ml on (b) (6) the day the subject exited the trial.

**Figure 3: Line graph and point data for serum liver tests, hepatitis C antibody and HCV RNA**



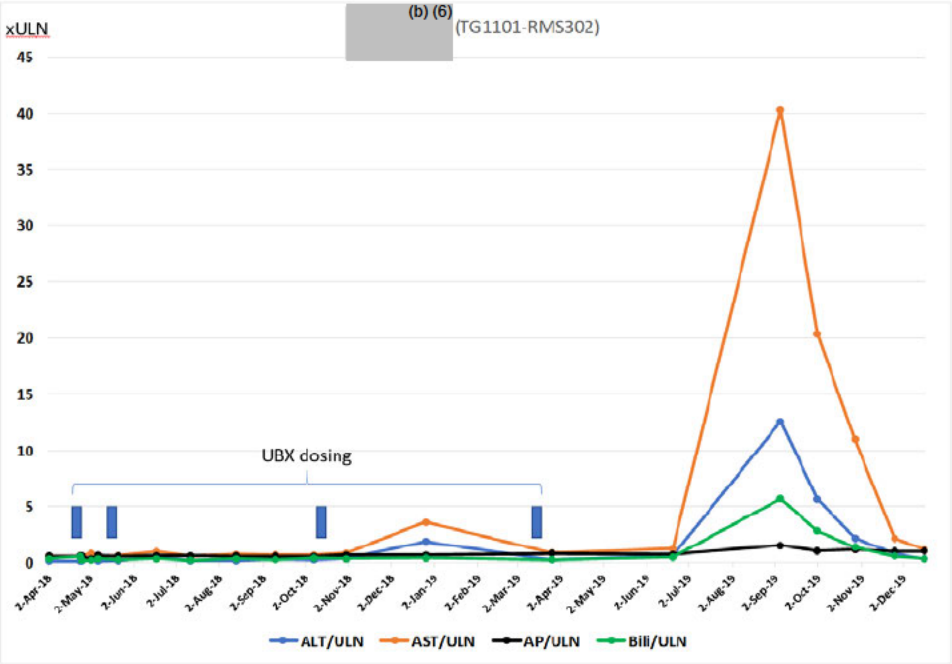

*Assessment*: This case is unlikely DILI due to UBX. The DILI Team concludes that this subject had acute HCV. Initial sawtooth enzyme pattern is a bit odd for acute hepatitis C, but subsequent fluctuations are consistent with possible lack of clearance---i.e., transition to chronicity. Otherwise, the RNA and anti-HCV Ab results are typical for acute hepatitis C with RNA appearing first and seroconversion later. In summary, the patient likely entered the trial with a recent HCV infection (detectable HCV RNA) but without presence of Anti-HCV Abs.

4.4.2.2 Subject (b) (6) (Study TG1101-RMS302): Unlikely DILI due to UBX.

*Summary*: This is a 46-year-old woman with MS. She enrolled in Russia.

She started UBX on (b) (6). Liver tests remained stable until after the third dose when a modest increase in ALT and AST was seen that resolved. (**Figure 4**) However, on (b) (6) 163 days after her fourth and final UBX dose and 499 days after UBX started, the subject had an acute rise in ALT and AST with a TB rise to 6.26 mg/dL. The narrative provided for this case is incomplete but a diagnosis of "chronic HBV infection" was made. However, no HBV test results (e.g., HBV DNA) are available for review.

**Figure 4: Line graph serum liver tests.**




*Assessment*: Although the narrative is limited, the DILI Team agrees with the applicant that this case is unlikely UBX-related DILI based on the long latencies from drug start (499 days) and protocol determined last dose (163 days). The enzyme elevation pattern would be consistent with a flare or reactivation of chronic HBV which can occur several months after anti-CD20 monoclonal therapy when B-cells are recovering.[10] Russia has an intermediate (2-4%) prevalence of HBsAg positivity.[11] The prevalence in the US is <2%. Anti-HBc status may be most pertinent to this case because the subject was likely HBsAg negative at screening. Reactivation of hepatitis B after anti-CD20 therapy in patients with only anti-HBc positivity pre-therapy is well documented. The protocol is unclear as to whether anti-HBc testing was part of subject screening prior to enrollment. The DILI Team could not find these data for this subject.

## 5.0 Assessment & Recommendations

5.1 Assessment: Ublituximab (UBX) is a recombinant, chimeric IgG1, monoclonal antibody directed at the CD20 antigen on B-lymphocytes. Like other anti-CD20 monoclonal biologics, UBX's binding is expected to result in B-cell destruction and marked decline in serum immunoglobulin levels. This decline

[10] LiverTox® https://www.ncbi.nlm.nih.gov/books/NBK548249/
[11] ResearchGate https://www.researchgate.net/figure/Global-prevalence-of-chronic-hepatitis-B-virus-HBV-infection-in-adults-Source-Centers_fig1_281682152

decreases immune-complexes that are hypothesized to cause multiple sclerosis (MS) disease progression. The Agency approved another anti-CD20 monoclonal (Ocrelizumab) for MS in 2017.

Non-clinical studies predict liver injury at or near UBX NOAEL dosing but hepatoxicity appeared in animals as part of multiple organ injuries and overall dose intolerance. Nevertheless, an immune mechanism was likely part of the injury based on ADA formation and lack of UBX reactive metabolites.

Five other anti-CD20 monoclonal antibodies have been approved by the Agency. Except for Ibritumomab, four of these monoclonal antibodies have labels describing HBV reactivation risk, but none warn of direct hepatotoxicity. Rituximab has rarely been reported to cause an immune-mediated liver injury, but attribution was not always clear in these reports.[12]

This BLA's two pivotal phase 3 trials exposed 545 subjects to UBX. There were no Hy's Law cases attributable to UBX. The two subjects on UBX who developed hepatocellular injury with jaundice had acute HCV infection and likely reactivation of HBV. There were only two additional subjects with possible DILI and ALT >5x ULN; however, neither had hyperbilirubinemia or symptoms. These latter two possible DILIs resolved quickly despite continued and complete UBX dosing per protocol.

DN2 raised a concern about the comparable ALT and AST elevations between UBX and teriflunomide (TFL) arms because TFL has a boxed warning for hepatotoxicity. We considered the concern of DN2, however, other factors led us to conclude that the concerns raised do not warrant holding up drug approval. TFL has a boxed warning for hepatotoxicity in part because of its structural similarity to leflunomide,[13] which is a "well-known cause of clinically apparent liver injury."[12] In contrast, anti-CD20 monoclonal antibodies are rarely associated with direct hepatotoxicity. Also, no clinically significant liver injuries (e.g., jaundice) were attributable to UBX, while the TFL trials had a hospitalized subject with jaundice, and DILI "could not be ruled out."[13]

Therefore, we do not see a DILI risk that would delay BLA approval. The number of subjects exposed to UBX is relatively small, but prior experience with other anti-CD20 monoclonal biologics mitigates concerns for a DILI risk arising in the larger post-market population. However, risk of HBV is likely similar to other marketed anti-CD20 monoclonals.

**5.2 Recommendations:**

a. Do not hold up approval for risk of liver injury with UBX.

[12] LiverTox® https://www.ncbi.nlm.nih.gov/books/NBK548249/
[13] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202992s000lbl.pdf

b. For product label we have the follow recommendations for consideration:
   i. Warning of heightened HBV reactivation risk prompting the need for screening of hepatitis B serologies (i.e., hepatitis B surface antigen, anti-hepatitis B core antibody) prior to UBX start.
   ii. Subjects who have either detectable serum HBsAg or Anti-HBc antibody, or both, should be referred to a liver specialist for hepatitis B prophylaxis prior to UBX initiation in accordance with guidelines for other anti-CD20 monoclonals.[14],[15],[16]
   iii. Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following UBX therapy. HBV reactivation has been reported up to 24 months following completion of therapy with rituximab, another anti-CD20 monoclonal.
   iv. Patients who develop reactivation of HBV while on UBX, should immediately discontinue UBX and receive appropriate treatment.

Ling Lan -S
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Date: 2022.09.19 08:40:52 -04'00'

Ling Lan, MD, PhD
Clinical Analyst, DILI Team, DHN
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Frank A. Anania, MD
(Acting) Director, DHN CDER/OND

[14] Loomba R, Liang JT. Gastroenterology, 2017
[15] Myint A, et al. Clinical Liver Disease, 2020
[16] Reddy KR, et al. Gastroenterology, 2015

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PAUL H HAYASHI
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# MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| Date of This Memorandum: | August 29, 2022 |
| Requesting Office or Division: | Division of Neurology 2 (DN 2) |
| Application Type and Number: | BLA 761238 |
| Product Name and Strength: | Briumvi (ublituximab-xiiy) injection, 150 mg/6 mL (25 mg/mL) |
| Applicant/Sponsor Name: | TG Therapeutics, Inc. |
| OSE RCM #: | 2021-1941-1 |
| DMEPA 2 Safety Evaluator: | Beverly Weitzman, PharmD |
| DMEPA 2 Acting Team Leader: | Stephanie DeGraw, PharmD |

## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on August 1, 2022 for Briumvi. The Division of Neurology 2 (DN 2) requested that we review the revised container label and carton labeling for Briumvi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

## 2 CONCLUSION AND RECOMMENDATIONS

The revised container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rational for concern, and proposed recommendations to minimize the risk for medication error in Section 3 (Table 1) for TG Therapeutics, Inc.

[a] Weitzman, B. Label and Labeling Review for Briumvi (BLA 761238). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUN 01. RCM No.: 2021-1941.

3. RECOMMENDATIONS FOR TG THERAPEUTICS, INC.

| Table 1. Identified Issues and Recommendations for TG Therapeutics, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| Container Label and Carton Labeling | | | |
| 1. | The appearance of the nonproprietary name "ublituximab xiiy" and dosage form "injection" lacks prominence commensurate with the proprietary name and is difficult to read. | As currently presented, the nonproprietary name does not appear to be presented in accordance with 21 CFR 201.10 (g)(2). Additionally, the finished dosage form "injection" lacks prominence. | Ensure the presentation of the nonproprietary name is at least half the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). In addition, to improve readability increase the prominence (i.e., font size) of the finished dosage form "injection." |
| 2. | The first letter of the proprietary name is not capitalized. Also, the placement of the graphic at the beginning of the proprietary name competes with the readability of the proprietary name. | This may lead to misinterpretation of the proprietary name (i.e., Obriumvi). | Consider capitalizing the first letter of the proprietary name (i.e., "Briumvi") as well as moving or decreasing the prominence of the graphic at the beginning of the proprietary name. |

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BEVERLY WEITZMAN
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STEPHANIE L DEGRAW
08/30/2022 09:48:43 AM

**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

# Division of Pediatrics and Maternal Health Review

**Date:** 8/29/2022 **Date consulted:** 5/25/2022

**From:** Catherine Roca, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

**Through:** Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

**To:** Division of Neurology 2 (DN2)

**Drug:** [TRADENAME] (ublituximab)

**BLA:** 761238

**Applicant:** TG Therapeutics, Inc.

**Subject:** Pregnancy and Lactation Labeling

**Proposed Indication:** Treatment of relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults

**Materials Reviewed:**

- Applicant's submitted background package and proposed labeling for BLA 761238
- DPMH consult request dated May 25, 2022, DARRTS Reference ID 4989669

**Consult Question:** "Please provide feedback regarding the proposed labeling with respect to potential for fetal harm and whether more stringent warnings are needed for ublituximab."

## INTRODUCTION AND BACKGROUND

On September 28, 2021, TG Therapeutics, Inc. submitted an original BLA for [TRADENAME] (ublituximab) for the treatment of relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. DN2 consulted DPMH on May 25, 2022, to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- [TRADENAME] (ublituximab), BLA 761238, was submitted for FDA review on September 28, 2021. It is proposed for the treatment of relapsing forms of multiple sclerosis and is not currently approved for use in any country.

Drug Characteristics[1]

- *Drug Class*- monoclonal IgG1 antibody that targets CD20 antigen expressed on the surface of pre-B and mature B lymphocytes
- *Mechanism of action*- The exact mechanism of action is unknown but is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ublituximab results in antibody-dependent cellular cytolysis, antibody-dependent cellular phagocytosis, and complement-mediated lysis.
- *Molecular weight*- 147 kilodaltons
- *Half-life*- the mean terminal half-life is estimated to be 22 days
- *Dosage and Administration* – ublituximab is administered as an intravenous infusion. The administration schedule is described in the Applicant's table below.

**Table 1. Recommended Dose, Infusion Rate, and Infusion Duration for RMS**

| | Amount and Volume | Infusion Rate | Duration[1] |
|---|---|---|---|
| First Infusion | 150 mg in 250 mL | • Start at 10 mL per hour for the first 30 minutes<br>• Increase to 20 mL per hour for the next 30 minutes<br>• Increase to 35 mL per hour for the next hour<br>• Increase to 100 mL per hour for the remaining 2 hours | 4 hours |
| Second Infusion (2 weeks later) | 450 mg in 250 mL | • Start at 100 mL per hour for the first 30 minutes<br>• Increase to 400 mL per hour for the remaining 30 minutes | 1 hour |
| Subsequent Infusions (once every 6 months)[2] | 450 mg in 250 mL | • Start at 100 mL per hour for the first 30 minutes<br>• Increase to 400 mL per hour for the remaining 30 minutes | 1 hour |

[1]Infusion duration may take longer if the infusion is interrupted or slowed.
[2]Administer the first Subsequent Infusion 6 months after the First Infusion.

[1] Applicant's proposed labeling

**REVIEW**

***PREGNANCY***

Multiple Sclerosis (MS) and Pregnancy

The prevalence estimates for MS vary between 58-95/100,000 in the United States.[2] Women are approximately 3 times more likely to have MS than men.[3] Rates of major perinatal complications, such as gestational diabetes, preeclampsia, thromboembolism, spontaneous abortion, congenital malformations, and placental abruption, do not differ between MS patients and the general population. Some studies show slightly higher rates of preterm delivery in pregnant women with MS.[4] Disease activity in multiple sclerosis generally decreases during the course of pregnancy with a 70% decrease in relapse rates during the third trimester; risk for relapse increases during the postpartum period.[5] If women experience a relapse during pregnancy, corticosteroids are generally the treatment of choice.[6]

Nonclinical Experience[7]

(b) (4)

The reader is referred to the full Pharmacology/Toxicology review by Barbara Wilcox, Ph.D. and Lois Freed, Ph.D.

*Reviewer Comment:*

(b) (4)

[2]https://www.cdc.gov/pcd/issues/2010/jan/08_0241 htm#:~:text=Prevalence%20estimates%20for%20MS%20vary,States%20(6%2D8).

[3] https://www nationalmssociety.org/What-is-MS/Who-Gets-MS

[4] Levin S, Rimmer K, Vargas WS. Neuroimmunologic disorders in pregnancy. Handbook of Clinical Neurology. 2020; 173(3):105-123.

[5] Levin S, Rimmer K, Vargas WS. Neuroimmunologic disorders in pregnancy. Handbook of Clinical Neurology. 2020; 173(3):105-123.

[6] Varyte G, et al. Pregnancy and multiple sclerosis: an update on the disease modifying treatment strategy and a review of pregnancy's impact on disease activity. Medicina. 2020;56(2):49.

[7] Sponsor's submitted draft labeling

(b) (4)

Review of Pregnancy Cases in Clinical Trials (See Appendix A for details)
There were 12 pregnancies reported during the clinical trials, three of which were due to a female partner of a male subject. Ten pregnancies occurred in in the ublituximab-exposed group and 2 in the teriflunomide[8]-exposed group.
Of the ten ublituximab-exposed pregnancies there were:

- Three pregnancies carried to term with live-born infants without complications (one was exposure via the father)
- One ectopic pregnancy that was complicated with purulent salpingitis with abdominal abscess and peritonitis resulting in maternal death
- Three elective abortions (one was exposure via the father). No fetal malformations were described.
- Three subjects withdrew consent, and the pregnancy outcomes are unknown (one was exposure via the father)

In the teriflunomide-exposed group, there were:

- One spontaneous abortion
- One elective abortion

Review of Literature
*Applicant's Review of the Literature:*
The Applicant did not provide a review of the published literature.

*DPMH Review of Literature:*
DPMH performed search of the published literature using Reprotox, PubMed and Embase databases and the search terms, "ublituximab" and "pregnancy," "congenital malformations," and "pregnancy outcomes."

No references or cases were found in the search of the published literature.

*Reviewer comment:*
*Ublituximab is not approved for any indication; published literature on its effects in pregnancy are not available. Data from clinical trials did not reveal any congenital malformations in the exposed pregnancies; however, these data are insufficient to make a safety determination regarding use of ublituximab during pregnancy. Preclinical studies in non-human primates resulted in maternal toxicity and death, and also resulted in increased fetal loss, limb malformations and brain necrosis. At the time of this review, the pharmaco-toxicology review was not finalized. However, discussions with the pharmaco-toxicology reviewer indicate that a safety margin cannot be determined for the enhanced pre- and postnatal study in non-human primates. Based on the nonclinical data, DPMH recommends a Warnings and Precautions for embryofetal toxicity be added to the labeling.*

[8]Teriflunomide is a pyrimidine synthesis inhibitor indicated for the treatment of relapsing forms of MS. Teriflunomide has a boxed warning for embryofetal toxicity and a pregnancy contraindication.

*In addition, based on the risks of B-cell depletion and the potential for embryofetal toxicity, language in Subsection 8.3 should include language recommending pregnancy testing prior to initiating therapy and the use of contraception in females of reproductive potential.*

***LACTATION***

Nonclinical Experience

The presence of ublituximab in animal milk was not described in the Sponsor's toxicology or nonclinical written summary document.

Review of Clinical Trials Cases

No cases of lactating women were described in the clinical trials.

Review of Literature

*Applicant's Review of the Literature*

The Applicant did not provide a review of the published literature.

*DPMH Review of the Literature.*

DPMH performed a search of the published literature using the terms "ublituximab," and "breastfeeding," or "lactation," using the PubMed, Embase, Reprotox, LactMed, and HalesMeds.com.

Ublituximab is not referenced in LactMed or HalesMeds.com.

No reports of cases related to lactation were found in the published literature.

*Reviewer comment:*

*The applicant did not provide a review of the literature; however, no cases related to lactation were found in the DPMH search of the literature. Maternal IgG is known to be present in human milk; however, monoclonal antibodies have poor oral bioavailability. Consequently, the systemic absorption to ublituximab is expected to be low but has not been studied. OCREVUS (ocrelizumab)[9] and KESIMPTA (ofatumumab)[10] have permissive language in their labeling. A recently published abstract of a lactation study of 23 women taking ocrelizumab also demonstrated low levels of ocrelizumab in breast milk (estimated mean infant dosage of 24 mcg/kg/day) and no adverse effects on the infants.[11] While RITUXAN[12] labeling recommends against breastfeeding, Hale's Medications and Mother's Milk[13] rates Rituximab as L3-Limited Data, Probably Compatible and notes that the relative infant dose found in a lactation study was 0.08-0.053% of the maternal weight-adjusted dose.[14] The Sponsor is proposing permissive language for ublituximab labeling. This seems reasonable, based on the properties of*

[9] OCREVUS (ocrelizumab) package insert, approved 12/14/2020, Drugs@FDA

[10] KESIMPTA (ofatumumab) package insert, approved 8/20/2020, Drugs@FDA

[11] Andersen A, et al. Ocrelizumab in postpartum women with multiple sclerosis: low transfer into breast milk and reassuring infant development in a multicenter cohort. ACTRIMS 2022 Forum; 2/25/2022: Session PS2 https://www.abstractsonline.com/pp8/#!/10495/presentation/495.

[12] RITUXAN (rituximab), package insert, approved 12/17/2021, Drugs@FDA

[13] https://www.halesmeds.com/, accessed 7/5/2022

[14] Krysko KM, et al. Minimal breastmilk transfer of rituximab, a monoclonal antibody used for neurological conditions. Neurol Neuroimmunol Neuroinflamm. 2019; 7(1):e637

*ublituximab (high molecular weight, low oral bioavailability); however, the Sponsor should perform a lactation study in lactating women being treated with ublituximab to obtain data on the presence of ublituximab in milk and the effects on the breastfed infant.*

***FEMALES AND MALES OF REPRODUCTIVE POTENTIAL***

Nonclinical Experience

No specific studies have been conducted to evaluate potential effects on fertility; however, no adverse effects on male or female reproductive organs were observed in the 26-week repeat-does toxicity study in cynomolgus monkeys.

Review of Clinical Trials Cases

No cases of infertility were described in the Summary of Clinical Safety.

Review of Literature

*Applicant's Review of Literature*

The applicant did not provide a review of the literature.

*DPMH Review of Literature:*

DPMH performed search of the published literature using Reprotox, PubMed and Embase databases and the search terms, "ublituximab" and "fertility," "infertility," and "hormonal contraceptives."

No cases related to fertility or hormonal contraceptives were found in the literature search.

*Reviewer comment:*

*The Applicant did not provide a review of the literature; however, there are no references related effects of ublituximab on fertility or hormonal contraceptives in the published literature. Nonclinical data do not describe adverse effects on reproductive organs in cynomolgus monkeys. Given the nonclinical data on adverse effects related to use of ublituximab in pregnant cynomolgus monkeys, including fetal loss and fetal malformations, Subsection 8.3, with subheadings for pregnancy testing and contraception, should be included in labeling.*

*DPMH discussed the duration of contraception use with the DN2 Clinical Pharmacology Team, who recommended a six-month duration of contraception after the last dose to maintain consistency with approved products (ocrelizumab and ofatumumab) in the same class with similar pharmacokinetic profiles and pharmacodynamic effects on CD20 cells. DPMH agrees with this duration of contraception use.*

**DISCUSSION AND CONCLUSIONS**

Pregnancy

Data on the effects on ublituximab on human pregnancy are limited to a few cases during the clinical trials. Preclinical studies in non-human primates resulted in maternal toxicity and death, and also resulted in increased fetal loss, limb malformations and brain necrosis. At the time of this review, the pharmaco-toxicology review was not finalized. However, discussions with the pharmaco-toxicology reviewer indicate that a safety margin cannot be determined for the enhanced pre- postnatal study in non-human primates. Based on the animal data, DPMH

recommends a Warning and Precaution for embryofetal toxicity be added to labeling. Since the limited human pregnancy reports have not demonstrated the birth defects observed in animal studies and since there is no clear mechanism to explain the birth defects observed in animal reproduction studies, DPMH does not recommend a pregnancy Contraindication or Boxed Warning at this time.

DPMH also recommends pregnancy testing prior to initiating therapy and the use of effective contraception by females of reproductive potential during therapy and for 6 months after the last dose. Based discussions between DPMH and the DN2 Clinical Pharmacology Team, contraception will be required for 6 months after the last dose to maintain consistency with approved products (ocrelizumab and ofatumumab) in the same class with similar pharmacokinetic profiles and pharmacodynamic effects on CD20 cell. DPMH recommends including Pregnancy Testing and Contraception subheadings in subsection 8.3.

Ublituximab is an IgG1 monoclonal antibody. Similar to the Agency's approach to labeling for other monoclonal antibodies, labeling will include information under 8.1 Risk Summary and Clinical Considerations about the active transport of monoclonal antibodies across the placenta and the potential for transient peripheral B-cell depletion and lymphocytopenia, which has been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. Labeling will note that the administration of live vaccines to neonates and infants exposed to [TRADE NAME] *in utero* should be avoided until B-cell recovery occurs.

Ublituximab is proposed for the treatment of MS, which occurs in females of reproductive potential. Although use in pregnancy is not recommended, unexpected pregnancy exposures are likely to occur and a comparative pregnancy registry study and pregnancy outcomes study using a different study design (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) have been required for similar antiCD20 antibodies.[15] DPMH recommends a comparative pregnancy registry study and pregnancy outcomes study using a different study design (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) be completed as post-marketing requirements.

Lactation

There are no data on the presence of ublituximab in human or animal milk, effects on the breastfed infant or effects on milk supply. Ublituximab is a typical IgG1 monoclonal antibody, which should behave similarly to endogenous IgG1. Therefore, similar to the Agency's approach for labeling for other monoclonal antibodies, labeling will include information under 8.2 that notes "Maternal IgG and monoclonal antibodies are transferred in human milk." Similar to the Agency's approach for other anti-CD20 antibodies, labeling will also note that "the effects of local gastrointestinal exposure and the potential for absorption of ublituximab to lead to B-cell depletion in the infant is unknown." The applicant has proposed permissive lactation language; this is reasonable based on low oral bioavailability of ublituximab.

[15] KESIMPTA (ofatumumab) approval letter, dated 8/20/2020, DARRTS Reference ID 4659303

Ublituximab will be used in females of reproductive potential. A milk-only lactation study in breastfeeding patients taking ublituximab is recommended as a postmarketing requirement to determine the amount of transfer into breastmilk and the effects on the breastfed infant.[16]

Females and Males of Reproductive Potential

There are no data on the effects of ublituximab on human fertility. Nonclinical data do not describe adverse effects on reproductive organs in cynomolgus monkeys. The animal fertility data may remain in Section 13.

Nonclinical data described adverse effects when ublituximab is administered to cynomolgus monkeys during pregnancy, including fetal loss and fetal malformations. Based on the nonclinical data, subsection 8.3 should include subheadings for pregnancy testing and contraception.

**POSTMARKETING REQUIREMENT (PMR) RECOMMENDATIONS**

- Conduct prospective pregnancy exposure registry cohort analyses in the US (b) (4) that compares the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to ublituximab during pregnancy with a control population of women with multiple sclerosis who have not been exposed to ublituximab before or during pregnancy. (b) (4)
- Conduct an additional pregnancy outcomes study that uses a different study design (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, (b) (4), preterm births, small-for-gestational age (b) (4) in women exposed to ublituximab during pregnancy compared to an unexposed control population.
- Perform a lactation study (milk only) in in lactating women who have received ublituximab to assess concentrations of ublituximab in breast milk (b) (4) and (b) (4) the effects on the breastfed infants

**LABELING RECOMMENDATIONS**

DPMH revised subsections 5.2, 5.3, 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final BLA action for final labeling.

3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[16] FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design, published May 9, 2019. https://www.fda.gov/media/124749/download

APPENDIX A. Cases of Pregnancies from Clinical Trials

**Table 1: List of Subjects With Pregnancy in the Phase III and Phase II Studies (Safety Population)**

| Study ID | Treatment Group | Subject ID | Onset Date | Outcome | Comments |
|---|---|---|---|---|---|
| TG1101-RMS301 | Ublituximab | [redacted] | [redacted] | Elective abortion | Date of abortion: [redacted] |
| TG1101-RMS301 | Ublituximab | | | Full-term delivery healthy male | Date of delivery: [redacted] |
| TG1101-RMS301 | Ublituximab | | | Unknown - ICF withdrawn | The subject had already completed treatment at the time of conception (last dose: [redacted]. |
| TG1101-RMS301 | Ublituximab | | | Elective abortion | Date of abortion: [redacted]<br>TEAE of ectopic pregnancy<br>The subject underwent an elective abortion with left-sided tubotomy and salpingostomatoplasty. Later, it was complicated with left-sided salpingitis, abdominal abscess, and peritonitis that led to the subject's death on [redacted] |
| TG1101-RMS301 | Teriflunomide | | | Spontaneous abortion | Date of abortion: [redacted] |
| TG1101-RMS302 | Ublituximab | | | Unknown - ICF withdrawn | Subject withdrew consent |
| TG1101-RMS302 | Teriflunomide | | | Elective abortion | Date of abortion: [redacted] |
| TG1101-RMS302 | Ublituximab | | | Elective abortion | Date of abortion: [redacted] |
| TG1101-RMS302 | Ublituximab | | | Elective abortion | Date of abortion: [redacted] |
| TG1101-RMS302 | Ublituximab | | | Unknown - ICF withdrawn | Female partner withdrew consent for further follow-up |
| TG1101-RMS302 | Ublituximab | | | Full-term delivery healthy female | Date of delivery: [redacted] |
| TG1101-RMS302 | Ublituximab | | | Full-term delivery healthy male | Date of delivery: [redacted] |

| Study ID | Treatment Group | Subject ID | Onset Date | Outcome | Comments |
|---|---|---|---|---|---|
| TG1101-RMS201 | Ublituximab | (b) (6) | | Full-term delivery healthy female | Date of delivery: (b) (6)<br>TEAE of pregnancy |
| TG1101-RMS201 | Ublituximab | | | Full-term delivery healthy male | Date of delivery: (b) (6)<br>TEAE of pregnancy of partner |

Sources: ISS, Listing 2.7.4.A.6 and Listing 2.7.4.B.3.13

Abbreviations: ICF, informed consent form; ID, identification; ISS, Integrated Summary of Safety; TEAE, treatment-emergent adverse event.

**APPENDIX B - Comparison of labeling from other anti-CD20 antibody products.**

| Section of Labeling | RITUXAN (Rituximab) | KESIMPTA (Ofatumumab) | OCREVUS (Ocrelizumab) | Ublituximab (proposed by Sponsor) |
|---|---|---|---|---|
| **Warnings & Precautions** | Embryofetal Toxicity<br>"Based on human data can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in utero. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving rituximab and for 12 month after the last dose." | Fetal Risk<br>Based on animal data, KESIMPTA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to KESIMPTA in utero. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving KESIMPTA and for at least 6 months after the last dose. | No Warnings and Precautions for embryofetal toxicity | (b) (4) |
| **Pregnancy 8.1 Risk Summary** | Based on human data Rituxan can cause adverse developmental outcomes including B-cell lymphocytopenia in infants exposed to Rituxan in-utero. In animal reproductive studies, intravenous administration of rituximab to pregnant cynomolgus monkeys during the period of organogenesis caused lymphoid B-cell depletion in the newborn offspring at doses resulting in 80% of the | There are no adequate data on the developmental risk associated with the use of KESIMPTA in pregnant women. Ofatumumab may cross the placenta and cause fetal B-cell depletion based on findings from animal studies. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to KESIMPTA have not been studied in clinical trials. The potential duration of | OCREVUS is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier. There are no adequate data on the developmental risk associated with the use of OCREVUS in pregnant women. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following | |

| | | | | |
|---|---|---|---|---|
| | exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Advise pregnant women of the risk to a fetus. | B-cell levels in infants exposed to ofatumumab in utero and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown. Avoid administering live vaccines to neonates and infants exposed to KESIMPTA in utero until B-cell recovery occurs.<br>Following administration of ofatumumab to pregnant monkey, increased mortality, depletion of B-cell populations and impaired immune function were observed in offspring, in the absence of maternal toxicity, at plasma levels substantially higher than that in humans. | maternal exposure to OCREVUS have not been studied in clinical trials. The potential for B-cell depletion in such infants, and the impact of B-cell depletion on vaccine safety and effectiveness in unknown.<br>Following administration of ocrelizumab to pregnant monkeys at doses similar to or greater than those used clinically increased perinatal mortality, depletion of B-cell populations, renal, bone marrow, and testicular toxicity were observed in the offspring in the absence of maternal toxicity. | (b) (4) |
| **Data- Human** | Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than 6 months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero. | No human data subheading | No human data subheading | |
| **Data- Animal** | An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via the intravenous route during early gestation | Intravenous administration of ofatumumab (weekly doses of 0, 20, or 100 mg/kg) to pregnant monkeys during the period of organogenesis (gestation days 20-50) resulted in no adverse effects on embryofetal development; however, B-cell depletion was | Following intravenous administration of OCREVUS to monkeys during organogenesis (loading doses of 15 or 75 mg/kg on gestation days 20, 21, and 22, followed by weekly doses of 20 or 100 mg/kg), depletion of B- | |

| | | | | |
|---|---|---|---|---|
| | (organogenesis period; post coitum (PC) days 20-50). Rituximab was administer as loading doses on PC days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then on PC days 29, 36, 43, and 50 at 20, 50, or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.<br><br>A subsequent pre- and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. | observed in fetuses at both doses when assessed on gestational day 100. Plasma exposure ($C_{ave}$) at the no effect dose (100 mg/kg) for adverse effects on fetal development was greater than 5000 times that in humans at the exposure ($C_{ave}$) at the low-effect dose (20 mg/kg). A no effect dose for effects on B-cells was not identified; plasma exposure ($C_{ave}$) at the low-effect dose (20 mg/kg) was approximately 780 times that in humans at the recommended human maintenance (RHMD) of 20 mg/month.<br>Intravenous administration of ofatumumab (5 weekly doses of 0, 10, and 100 mg/kg, followed by biweekly doses of 0, 3, and 20 mg/kg) to pregnant monkeys throughout pregnancy resulted in no adverse effects on the development of offspring. However, postnatal death, B-cell depletion, and impaired immune function were observed in the offspring at the no-effect dose (100/20 mg/kg) for adverse developmental effects was approximately 500 times that in humans at the RHMD. A no-effect level for mortality and immune effects in offspring was not established because of the limited number of evaluable offspring at the low dose. | lymphocytes in lymphoid tissue (spleen and lymph nodes was observed in fetuses at both doses.<br>Intravenous administration of OCREVUS (three daily loading doses of 15 or 75 mg/kg, followed by weekly doses of 20 or 100 mg/kg) to pregnant monkeys throughout the period of organogenesis and continuing through the neonatal period resulted in perinatal deaths (some associated with bacterial infections), renal toxicity (glomerulopathy and inflammation), lymphoid follicle formation in the bone marrow and severe decreases in circulating B-lymphocytes in neonates. The cause of the neonatal deaths is uncertain; however, both affected neonates were found to have bacterial infections.<br>Reduced testicular weight was observed in neonates at the high dose.<br>A no-effect dose for adverse developmental effects was not identified; the doses tested in monkeys are 2 and 10 times the recommended dose of 600 mg, on a mg/kg basis. | (b) (4) |

| | | | | |
|---|---|---|---|---|
| | Subsets of pregnant females were treated from PC Day 20 through postpartum Day 28. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum | | | |
| Lactation | There are limited data on the presence of rituximab in human milk and the effect on the breastfed child and there are no data on the effect on milk production. Rituximab is detected in the milk of lactating cynomolgus monkeys, and maternal IgG is present in human breast milk. Rituximab has also been reported to excreted in low concentrations in human breast milk. Given that the clinical significance of this finding for children is not known, advise women not to breastfeed during treatment with Rituxan and for 6 months after the last dose due to the | There are no data on the presence of ofatumumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Human IgG is excreted in human milk and the potential for absorption of ofatumumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KESIMPTA and any potential adverse effects on the breast fed infant from KESIMPTA or the underlying maternal condition. | There are no data on the presence of ocrelizumab in human milk, the effects on a breastfed infant, or the effects on milk production. Ocrelizumab was excreted in the milk of ocrelizumab-treated monkeys. Human IgG is excreted in human milk, and the potential for absorption of ocrelizumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OCREVUS and any potential adverse effect on the breastfed infant from OCREVUS or from the underlying maternal condition. | (b) (4) |

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|---|---|---|---|---|
| | potential serious adverse reactions in breastfed children. | | | |
| **8.3 Females and Males of Reproductive Potential** | <u>Pregnancy Testing</u><br>Verify pregnancy status in females of reproductive potential prior to initiating Rituxan.<br><u>Contraception</u><br>Advise females of reproductive potential to use effective contraception during treatment with Rituxan and for 12 months after the last dose. | <u>Contraception</u><br>Females of childbearing potential should use effective contraception while receiving KESIMPTA and for 6 months after the last treatment of KESIMPTA. | <u>Contraception</u><br>Women of childbearing potential should use effective contraception while receiving OCREVUS and for 6 months after the last infusion of OCREVUS. | (b) (4) |

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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CATHERINE A ROCA
08/29/2022 05:07:58 PM

MIRIAM C DINATALE
08/29/2022 05:12:25 PM

LYNNE P YAO
08/30/2022 03:32:17 PM

# Clinical Inspection Summary

| | |
|---|---|
| **Date** | 07/12/2022 |
| **From** | Cara Alfaro, Pharm.D., Clinical Analyst<br>Phillip Kronstein, M.D., Team Leader<br>Kassa Ayalew, M.D., M.P.H., Division Director<br>Good Clinical Practice Assessment Branch<br>Division of Clinical Compliance Evaluation<br>Office of Scientific Investigations |
| **To** | Rania Younes, Regulatory Project Manager<br>Laura Baldassari, M.D., Medical Officer<br>Paul Lee, M.D., Team Leader<br>Division of Neurology 2<br>Office of Neuroscience |
| **BLA #** | 761238 |
| **Applicant** | TG Therapeutics |
| **Drug** | Ublituximab |
| **NME** | Yes |
| **Proposed Indication** | Treatment of relapsing multiple sclerosis (MS) |
| **Consultation Request Date** | 11/17/2021 |
| **Clinical Inspection Summary Goal Date** | 5/28/2022, extended to 6/24/2022, 7/12/2022 |
| **Priority/Standard Review** | Standard |
| **Action Goal Date** | 12/28/2022 |
| **PDUFA Date** | 9/28/2022, extended to 12/28/2022 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Dinčić, Habek, Robertson, and Wray were inspected in support of this BLA and covered Protocols TG1101-RMS301 and TG1101-RMS302. A For-Cause inspection of the sponsor, TG Therapeutics, had been conducted in January 2021 covering their pharmacovigilance program and safety reporting for the ublituximab development program. The clinical investigator inspections identified some protocol deviations as noted below, but all the primary efficacy endpoint data (MS relapses, Expanded Disability Status Scale [EDSS] scores, and Functional System [FS] scores) for these sites could be verified. Although there were some potential unblinding events described below, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The inspection of Dr. Wray identified that unblinded MRI reports containing multiple sclerosis (MS) pathology results were sent from the local MRI facility to the clinical site for 3 of 8 randomized subjects. These unblinded MRI reports were reportedly reviewed by the Treating Neurologist. Per protocol, MRI reports sent to the clinical sites were to

include only "non-MS pathology" results to allow for safety monitoring. These protocol deviations were included in the BLA submission. We recommended that the review division request that the sponsor provide a comprehensive listing of all potential unblinding events for both protocols and an assessment of the potential impact of these events on efficacy analyses. The sponsor responded that there were 12 unblinded MRI events occurring in 9 subjects in Protocol TG1101-RMS301 and 16 unblinded MRI events occurring in 7 subjects in Protocol TG1101-RMS302. Additionally, there were 4 instances in 4 subjects in which EDSS scores or relapse information was shared with the Treating Neurologist in Protocol TG1101-RMS301. Intentional unblinding for management of subject safety occurred in 6 subjects; no further efficacy data was collected following this intentional unblinding. The sponsor submitted a sensitivity analysis excluding all subjects with unintentional and intentional unblinding.

To ensure confidence that all unblinded MRI events were identified during the conduct of the protocols, we recommend that the review division request that the sponsor describe the blinding/redaction process followed by local MRI facilities for removing MS pathology from MRI results prior to sending to the clinical site as well as the quality control process followed by the CRO and/or sponsor to ensure that this blinding/redaction was completed prior to sending MRI reports to the clinical sites.

The For-Cause inspection of the sponsor found that the sponsor did not have a formalized standard operating procedure (SOP) in place for assessing safety during the conduct of Protocols TG1101-RMS301 and TG1101-RMS302. Additionally, the rationale for assessing causality for safety cases was unclear, as was noted by both the DSMB and the review division at the time the studies were conducted. In August 2020, the review division had requested that the sponsor submit all infections and deaths as IND safety reports, regardless of causality. The sponsor reassessed some safety cases based on communications with the review division, but it does not appear that all prior cases were reassessed. The Good Clinical Practice Compliance Oversight Branch of OSI conveyed this information to the review division after the inspection was completed. The BLA submission includes all aggregate safety data, regardless of whether individual cases had been previously submitted as IND safety reports. The risk of infections is included in the Warnings and Precautions section of proposed labeling.

## II. BACKGROUND

Ublituximab injection for intravenous use is being developed under BLA 761238 (IND 127265) for the treatment of relapsing forms of multiple sclerosis (MS).

The sponsor has submitted two Phase 3 studies of identical design, TG1101-RMS301 and TG1101-RMS302, to support the efficacy and safety of ublituximab for the treatment of relapsing MS.

Protocol TG1101-RMS301

*Title:* "Phase III: UbLiTuximab in multiple sclerosis treatment effects (ULTIMATE I STUDY)"

*Subjects*: 548

*Sites*: 57 sites; Eastern Europe (34 sites), United States (12 sites), Middle East/Central Asia (7 sites), Western Europe (4 sites)

*Study Initiation and Completion Dates*: 9/19/2017 – 11/6/2020

*Database Lock Date*: 11/23/2020

This was a randomized, double-blind, double-dummy, active-controlled study in subjects with relapsing multiple sclerosis (RMS). Main eligibility criteria included males or females 18 to 55 years of age; diagnosis of RMS; ≥2 relapses in prior 2 years or 1 relapse in the year prior to screening and/or ≥1 gadolinium (Gd) enhancing lesion; documented MRI of brain with abnormalities consistent with MS; Expanded Disability Status Scale (EDSS) score 0-5.5 (inclusive) at screening; B cell counts >5% of total lymphocytes; and neurological stability >30 days prior to screening and baseline.

The study was comprised of 3 phases:

Screening – Day -28 to Day 0
Determination of subject eligibility.

Double-blind Treatment Phase – Week 1 to Week 96
Subjects were randomized (1:1) to one of the following arms:

| | Week 1 Day 1 | Week 3 Day 15 | Week 24 | Week 48 | Week 72 | Week 96 |
|---|---|---|---|---|---|---|
| Ublituximab (UTX) + placebo (oral) | UTX 150 mg/4 hr | UTX 450 mg/1 hr | UTX 450 mg/1 hr | UTX 450 mg/1 hr | UTX 450 mg/1 hr | |
| | Oral Placebo daily from Week 1 Day 1 until last day of Week 95 | | | | | |
| Teriflunomide + placebo (infusion) | Teriflunomide 14 mg daily from Week 1 Day 1 until last day of Week 95 | | | | | |
| | Infusion Placebo | Infusion Placebo | Infusion Placebo | Infusion Placebo | Infusion Placebo | |

Subjects who experienced new or worsening neurologic symptoms were instructed to contact the Treating Neurologist within 48 hours of symptom onset. The Examining Neurologist (EDSS rater) was also notified to perform additional assessments. Within 7 days of the subject reporting the suspected relapse to the Treating Neurologist, the subject was to be assessed independently by both the Treating and Examining Neurologists. Treatment of relapses could proceed at the discretion of the Treating Neurologist only after the Examining Neurologist completed the examination (the

Treating Neurologist was not to know the results of the EDSS assessment). If the decision was made to treat the relapse, the Treating Neurologist could use intravenous methylprednisolone (1 g/day for 3 to 5 days), and this would not affect the subject's eligibility to continue in the study.

Follow-up Phase – Week 100 to Week 116
After the double-blind treatment phase, subjects were followed for another 20 weeks to enable teriflunomide elimination monitoring. During this phase, adverse events were assessed.

The ***primary efficacy endpoint*** was the independent relapse adjudication panel (IRAP) confirmed MS annualized relapse rate (ARR) per subject year, comparing ublituximab to teriflunomide. A MS relapse was defined as new or worsening neurological symptoms lasting ≥24 hours with the absence of fever, injury, infection, or adverse reactions to medications and accompanied by new neurological findings upon examination by the Examining Neurologist. MS relapses had to meet the following EDSS or Functional System (FS) score criteria:

- An increase of ≥0.5 in the EDSS score *or*
- An increase of ≥2 points on one of the Functional System (FS) scores *or*
- An increase of ≥1 point on two or more of the FS scores

Protocol TG1101-RMS302

*Title:* "Phase III: UbLiTuximab in multiple sclerosis treatment effects (ULTIMATE II STUDY)"

*Subjects*: 545

*Sites*: 47 sites; Eastern Europe (32 sites), United States (10 sites), Western Europe (5 sites)

*Study Initiation and Completion Dates*: 8/25/2017 – 11/12/2020

*Database Lock Date*: 11/23/2020

The design and efficacy endpoints for this protocol were the same as for Protocol TG1101-RMS301.

**Rationale for Site Selection**

The majority of subjects participating in these two studies were enrolled at sites in Eastern Europe. Sites chosen were among the highest enrolling Eastern European sites with no prior inspection history. The highest enrolling domestic sites were also chosen to verify domestic clinical trial data.

## III. RESULTS

1. **Evica Dinčić, M.D.**
   **Site #138102**
   Military Medical Academy
   Crnotravska 17
   Belgrade, 11 000
   Serbia
   ***Inspection Dates***: 3/21/2022 to 3/25/2022

   At this site for Protocol TG1101-RMS301, 27 subjects were screened and 23 subjects were randomized and completed the study.

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IEC/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse events, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (date of MS relapse, EDSS scores, FS scores).

   At this site, Dr. Dinčić was the Treating Neurologist and two other neurologists were Examining Neurologists who performed examinations for the EDSS and FS scales. Examining Neurologists recorded EDSS and FS scores on paper and entered data into the EDC system. The inspection verified that all subjects had contacted the site within 48 hours of the onset of MS relapse symptoms and were evaluated by both the Treating and Examining Neurologists within 7 days.

   Seven subjects, two randomized to ublituximab and five randomized to teriflunomide, experienced MS relapses that were confirmed by the Independent Relapse Adjudication Panel (IRAP). Subject # (b) (6), randomized to ublituximab, experienced an MS relapse that was not an IRAP-confirmed relapse. The dates of MS relapse were confirmed, and the EDSS and FS scores recorded on paper source were verified against the sponsor data listings; no discrepancies were identified.

   There were some adverse events that were not reported to the sponsor:
   - Subject # (b) (6), randomized to teriflunomide, experienced dyspepsia lasting 10 days during the follow-up period
   - Subject # (b) (6), randomized to teriflunomide, experienced dyspepsia lasting 3 days during the follow-up period
   - Subject # (b) (6), randomized to ublituximab, reported a headache occurring on one day during Week 95 which was treated with ibuprofen (also not reported).

   In addition, lymphocytopenia (Grades 2 and 3) was noted in at least three subjects, # (b) (6), which the CI did not report as she considered it to be related to the

premedication, dexamethasone. All three of these subjects were randomized to ublituximab.

One serious adverse event, COVID-19 pneumonia, occurred during the follow-up period in Subject # (b) (6) who was randomized to ublituximab. Consistent with the protocol, this SAE was reported to the sponsor within 24 hours of the study staff's awareness of the events. The narrative for this SAE is included in the BLA submission.

*Reviewer's comment: Three adverse events occurring in three of 23 randomized subjects were not reported to the sponsor. Two of the adverse events occurred during the follow-up period of the study in subjects randomized to teriflunomide. It is unlikely that exclusion of these adverse events would impact the overall safety assessment of the application. Per protocol, abnormal laboratory results were to be reported as adverse events. Therefore, lymphocytopenia should have been reported as an adverse event regardless of the presumed etiology. Lymphocytopenia is, however, reflected in the application in the results of the laboratory indices.*

**2. Mario Habek, M.D., Ph.D.**
**Site #238501**
Clinical Hospital Centre
Kispaticeva 12
Zagreb, 10 000
Croatia
***Inspection Dates***: 3/7/2022 - 3/11/2022

At this site for Protocol TG1101-RMS302, 31 subjects were screened, 27 were randomized, and 25 subjects completed the study. Two subjects discontinued the study due to withdrawal of consent.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IEC/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse events, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (date of MS relapse, EDSS scores, FS scores).

At this site, Dr. Habek was the Treating Neurologist and one other neurologist was the Examining Neurologist who performed examinations for the EDSS and FS scales.
The Examining Neurologist remained blinded to any results from the Treating Neurologist. Examining Neurologists recorded EDSS and FS scores on paper and entered data into the EDC system. The inspection verified that all subjects were evaluated by both the Treating and Examining Neurologists within 7 days of the onset of MS relapse symptoms.

Two subjects, Subject # (b) (6) randomized to ublituximab, and Subject # (b) (6) randomized to teriflunomide, experienced MS relapses that were confirmed by the Independent Relapse Adjudication Panel (IRAP). The dates of MS relapse were confirmed, and the EDSS and FS scores recorded on paper source were verified against the sponsor data listings; no discrepancies were identified.

Five adverse events occurring in 2 of 27 randomized subjects were not reported to the sponsor, and concomitant medications were taken for these adverse events which were also not reported to the sponsor (Table 1). Concomitant medications for an additional 4 subjects were also not reported to the sponsor (Table 1). These unreported concomitant medications, all of which were taken during the double-blind phase, were listed in diaries that were completed by the subjects.

**Table 1. Unreported Concomitant Medications and Adverse Events**

| Subject | Treatment Arm | Concomitant Medication | Dates | Reason for Use | Adverse Event Reported? |
|---|---|---|---|---|---|
| (b) (6) | Ublituximab | Albuterol | (b) (6) | FeNO test/asthma | N/A |
| | Ublituximab | Magnesium | | Mineral supplement | N/A |
| | Ublituximab | Cod liver oil | | Not documented | N/A |
| | | Pantoprazole | | AE Gastric Pain | No |
| | | Tramadol | | AE Headache | No |
| | Ublituximab | Diazepam | | AE Insomnia | No |
| | | Ibuprofen | | AE Headache | No |
| | | Naproxen | | AE Headache | No |
| | Teriflunomide | Anesthesia (unspecified) | | Dental procedures | N/A |
| | Teriflunomide | Magnesium | | Not documented | No |

*Reviewer comments: Concomitant medications for 6 of 27 (22.2%) randomized subjects were not reported to the sponsor. None of these were prohibited concomitant medications. For two*

*of these subjects, concomitant medications were taken for five adverse events that were also not reported to the sponsor. The review division may consider including these relatively minor adverse events in the overall safety analysis.*

**3. Derrick Robertson, M.D**
**Site #200106**
University of South Florida
13330 USF Laurel Drive
Tampa, FL 33612
***Inspection Dates***: 1/14/2022 – 1/26/2022

At this site for Protocol TG1101-RMS302, 14 subjects were screened, and 8 subjects were randomized and completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse events, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (date of MS relapse, EDSS scores, FS scores).

At this site, Dr. Robertson was the Treating Neurologist and one other neurologist was the Examining Neurologist who performed examinations for the EDSS and FS scales. The Examining Neurologist stated that they did not share EDSS or FS scores with the treating neurologist and they remained blinded to adverse events, concomitant medications, and laboratory results throughout the study. The Examining Neurologist recorded EDSS and FS scores on paper and entered data into the EDC system. The inspection verified that all subjects were evaluated by both the Treating and Examining Neurologists within 7 days of the onset of MS relapse symptoms.

Subject # (b) (6), randomized to teriflunomide, and Subject # (b) (6), randomized to ublituximab, experienced MS relapses that were confirmed by the Independent Relapse Adjudication Panel (IRAP). The dates of MS relapse were confirmed, and the EDSS and FS scores recorded on paper source were verified against the sponsor data listings; no discrepancies were identified. There was no evidence of under-reporting of adverse events.

**4. Sibyl Wray, M.D.**
**Site #100103**
Hope Neurology PLLC
2060 Lakeside Centre Way
Knoxville, TN 37922
***Inspection Dates*:** 1/10/2022 – 1/25/2022

At this site for Protocol TG1101-RMS301, 9 subjects were screened, 8 subjects were randomized, and 7 subjects completed the study. One subject discontinued the study due to withdrawal of consent.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse events, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (date of MS relapse, EDSS scores, FS scores).

At this site, Dr. Wray was the treating neurologist and two other neurologists were examining neurologists (EDSS raters) who performed examinations for the EDSS and FS scales. The inspection verified that all subjects were evaluated by both the treating and examining neurologists within 7 days of the onset of MS relapse symptoms.

Subject # (b) (6), randomized to ublituximab, experienced an MS relapse that was confirmed by the Independent Relapse Adjudication Panel (IRAP). Two subjects (# (b) (6) ), both randomized to teriflunomide, experienced MS relapses that were not IRAP-confirmed relapses. The dates of MS relapse were confirmed and the EDSS and FS scores recorded on paper source were verified against the sponsor data listings; no discrepancies were identified.

There was no evidence of under-reporting of adverse events. However, one SAE was reported late. Subject # (b) (6) informed study personnel on (b) (6) that she had been hospitalized for chest pain. Dr. Wray notified the sponsor of this SAE on (b) (6), approximately 3 months after the site was aware. Per protocol, the sponsor must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by study personnel.

Unblinded MRI results were reviewed by the Treating Neurologist for three subjects at this site. None of these three subjects experienced an IRAP-confirmed MS relapse. Per protocol, MRI scans were performed at screening and Weeks 12, 24, 48, and 96/Early discontinuation. The blinded central MRI analysis center (NeuroRx) was responsible for the MRI-related key secondary efficacy endpoints. In addition, all MRI scans were to be reviewed locally by a

radiologist for safety, and the MRI scan report containing only non-MS pathology was to be provided to the Treating Neurologist. For the following subjects, unblinded MRI results were sent to the site and reviewed by the Treating Neurologist and/or subject:

- Subject # (b) (6), randomized to teriflunomide, Week 24 MRI results were present with source documents and signed by the Treating Neurologist. The local radiology facility had sent the MRI scan report containing MS pathology to the site. During the inspection, the study coordinator stated that the MRI report was left attached to the outside of the subject's chart. The subject saw the MRI report, which indicated the presence of a new lesion. This unblinded MRI incident was included in the protocol deviation line listings, but the deviation description only stated that the Treating Neurologist signed the report.
- Subject # (b) (6), randomized to teriflunomide, Week 24 MRI results with MS pathology were filed in the subject's chart. This unblinded MRI incident was included in the protocol deviation line listings but was not further evaluated during the inspection.
- Subject # (b) (6), randomized to teriflunomide, Week 48 MRI results with MS pathology were present in the subject's source records and signed by the Treating Neurologist. This unblinded MRI incident was included in the protocol deviation line listing but was not further evaluated during the inspection.

A corrective action and preventive action (CAPA) plan written by the CRO (PRI) was available at the site. This CAPA was implemented in (b) (6) completed in (b) (6) and included the MRI issue as noted above for Subject # (b) (6). The CAPA did not include the other two subjects. The corrective action that was to be taken was for the site to contact the imaging facility and remind them only to include non-MS MRI findings. The date that the site contacted the MRI imaging facility is not known. The CAPA report notes that the CRO identified this issue for Subject # (b) (6) in (b) (6), approximately 7 months after the unblinded MRI scan report was sent to the site.

*Reviewer comments: For three of eight randomized subjects, unblinded MRI scan reports containing MS-pathology were sent to this site, reportedly reviewed by the Treating Neurologist, and, in one case, also seen by the subject. This was included in the protocol deviation line listings for the three subjects at the site. No similar protocol deviations for Study TG1101-RMS301 were noted at any other sites*

*We recommended that the review division request the sponsor to provide a comprehensive listing of all potential unblinding events for both protocols and an assessment of the potential impact of these events on efficacy analyses. The sponsor responded that there were 12 unblinded MRI events occurring in 9 subjects in Protocol TG1101-RMS301 and 16 unblinded MRI events occurring in 7 subjects in Protocol TG1101-RMS302. Additionally, there were 4 instances in 4 subjects in which EDSS scores or relapse information was shared with the*

*Treating Neurologist in Protocol TG1101-RMS301. Intentional unblinding for management of subject safety occurred in 6 subjects; no further efficacy data was collected following this intentional unblinding. The sponsor submitted a sensitivity analysis excluding all subjects with unintentional and intentional unblinding.*

*To ensure confidence that all unblinded MRI events were identified during the conduct of the protocols, we recommend that the review division request the sponsor to describe the blinding/redaction process followed by local MRI facilities for removing MS pathology from MRI results prior to sending to the clinical sites as well as the quality control process followed by the CRO and/or sponsor to ensure that this blinding/redaction was completed prior to sending MRI reports to the clinical sites.*

**TG Therapeutics**

The sponsor, TG Therapeutics, was not inspected as part of this BLA submission. A For-Cause inspection of TG Therapeutics was conducted from 1/19/2021 – 1/29/2021 covering, among other things, the two protocols for the above clinical investigator inspections, i.e., Protocols TG1101-RMS301 and TG1101-RMS302, conducted under IND 127265.

The sponsor inspection was initiated due to concerns that the Division of Neurology 2 had concerning the sponsor's criteria for the submission of IND safety reports, specifically with regard to serious infections, as well as the sponsor's assessments of expectedness and causality. Additionally, the review division had concerns regarding the late reporting of some fatalities occurring in clinical trials, as there were fatalities noted upon review of Development Safety Update Reports (DSURs) that had not been submitted as IND safety reports.

The review division brought these concerns to OSI in February 2020, but the inspection did not occur until 2021 due to COVID-19. Due to these concerns, in August 2020, the review division requested that the sponsor submit as IND safety reports, all infections, regardless of whether they were deemed serious or unexpected no later than 7 calendar days after receipt of the information. Additionally, the review division requested that the sponsor submit all reports of deaths, regardless of the sponsor's assignment of an association to the investigational product and irrespective of expectation no later than 7 calendar days after receipt of the information.

The focus of the inspection was on safety and adverse event reporting. Records reviewed included, but were not limited to, Standard Operating Procedures (SOPs), contracts, transfer of regulatory obligations (TOROs), monitoring plans, safety plans, monitoring reports, safety reports, DSMB meeting minutes, signal detection plans, and correspondence. The CRO, PSI CRO AG (Switzerland), was responsible for reporting serious and unexpected suspected adverse reactions (SUSARs) to foreign regulatory agencies, and the sponsor was responsible for reporting them to the FDA.

According to the sponsor, prior to April 2020, there was no formal SOP related to safety reporting and signal detection. Before implementation of the SOP, signal detection and safety risk management were conducted by both routine and ad-hoc review of the aggregate safety data across their clinical studies in preparation for investigational brochure updates, DSURs, and DSMB meetings. There was no formal documentation of these safety data reviews and an increased risk for serious infection was not identified in the MS program. However, the signal of a potential risk for infections in the MS program was raised in late 2019 by the DSMB (Protocols TG1101-RMS301/TG1101-RMS302) and the FDA. Per the review division's request in December 2019, the sponsor amended clinical study documents (informed consent forms, investigator brochure, protocols) for further awareness of this risk. During the inspection, causality assessments for nine IND safety reports submitted to the Agency were discussed with the sponsor. In general, it was unclear how causality assessments were determined for serious infections, including those leading to death.

The sponsor noted that after several information requests from the Agency in 2019 and 2020, they took a conservative approach and looked back at previously submitted safety reports to determine whether they needed to be reassessed. Cases chosen for reassessment were based on prior information requests from the review division. No new medical information was obtained in the reassessment of these cases. Some of these cases were changed from "not related" to "possibly related".

*Reviewer comments: The sponsor did not have a formalized standard operating procedure for assessing safety during the conduct of Protocols TG1101-RMS301 and TG1101-RMS302. Additionally, the rationale for assessing causality for safety cases was unclear, as was noted by both the DSMB and the review division. Of note, causality assessments of "not-related" do not meet reporting criteria, in the form of 7- or 15-day IND Safety Reports.*

*In August 2020, the review division had requested that the sponsor submit all infections and deaths as IND safety reports, regardless of causality. The sponsor reportedly reassessed some safety reports based on information requests from the review division, but it does not appear that all prior safety reports were reassessed. The Good Clinical Practice Compliance Oversight Branch in OSI conveyed this information to the review division after the inspection was completed. This BLA submission includes all aggregate safety data, regardless of whether individual cases had been previously submitted as IND safety reports. The risk of infections is included in the Warnings and Precautions section of proposed labeling.*

*{See appended electronic signature page}*

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

| | |
|---|---|
| Date of This Review: | June 1, 2022 |
| Requesting Office or Division: | Division of Neurology 2 (DN 2) |
| Application Type and Number: | BLA 761238 |
| Product Name and Strength: | Briumvi (ublituximab-wxyz)[a] injection, 150 mg/6 mL (25 mg/mL) |
| Product Type: | Single Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | TG Therapeutics, Inc. |
| FDA Received Date: | September 28, 2021 |
| OSE RCM #: | 2021-1941 |
| DMEPA 2 Safety Evaluator: | Beverly Weitzman, PharmD |
| DMEPA 2 Team Leader (Acting): | Stephanie DeGraw, PharmD |

[a] The nonproprietary name suffix has not been designated; therefore, "-wxyz" is used throughout this review as placeholder.

## 1 REASON FOR REVIEW

As part of the approval process for Briumvi (ublituximab-wxyz) 150 mg/6 mL (25 mg/mL), the Division of Neurology 2 (DN 2) requested that we review the proposed Briumvi prescribing information (PI), medication Guide (MG), container label and carton labeling for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

| Table 1. Materials Considered for this Label and Labeling Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B (N/A) |
| ISMP Newsletters* | C (N/A) |
| FDA Adverse Event Reporting System (FAERS)* | D (N/A) |
| PROPOSED REVISIONS TO SECTION 2 DOSAGE AND ADMINISTRATION (sections 2.3 and 2.6) | E |
| Labels and Labeling | F |

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), medication guide, container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 (Table 2) for the Division and in Section 5 (Table 3) for TG Therapeutics, Inc.

## 4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 2 (DN 2)

| Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| Prescribing Information (PI) and Medication Guide (MG) – General Issues | | | |
| 1. | The PI and MG do not contain the nonproprietary suffix placeholder "wxyz" in alignment with what is presented on the container label and carton labeling. | The nonproprietary 4-letter suffix has not yet been designated for this product. As such, the 4-letter suffix placeholder "wxyz" presented on the container and carton labeling should also be included in PI and MG. | We recommend including the nonproprietary 4-letter suffix placeholder "wxyz" in the proposed PI and MG. Once the nonproprietary name with a designated suffix has been found acceptable, the "wxyz" should be replaced with the designated suffix. |
| 2. | The placeholder, TRADENAME is used throughout the PI and MG labeling. | The proposed proprietary name, Briumvi was found acceptable on January 3, 2022.[b] | The placeholder, TRADENAME, should be replaced with the conditionally acceptable name, Briumvi, throughout the PI and MG labeling. |
| Highlights of Prescribing Information and Full Prescribing Information – Section 2 Dosage and Administration | | | |
| 1. | We note per the PI labeling, the Sponsor has not specified that this biologic product needs to be administered via an in-line filter. | If an in-line filter is required during administration, this information should be included in the PI to prevent medication errors related to administration. | We defer to Office of Pharmaceutical Quality (OPQ) to determine whether this biologic needs to be administered via in-line filter. If so, then we recommend this information be added to the labeling in the Dosage and Administration section of the HPI and Section 2.6 of the FPI as well as the carton labeling. |
| Highlights of Prescribing Information | | | |
| 1. | The product requires a specific diluent (that is, 0.9% Sodium Chloride Injection, USP) which is | We are concerned there is a risk for preparation errors related to using a wrong solution for dilution. | We recommend revising 4th bullet point in HL (Dosage and Administration) to remind readers to dilute Briumvi with |

[b] Weitzman, B. Proprietary Name Review for Briumvi (BLA 761238). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JAN 03. PNR ID No. 2021-1044724250

| Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | not stated in the Highlights of Prescribing Information (Dosage and Administration). | | 0.9% Sodium Chloride Injection, USP. For example, "Must be diluted in 0.9% Sodium Chloride Injection, USP prior to administration. (2.3, 2.6)" |
| 2. | In the Highlights of Prescribing Information (Dosage and Administration) the recommended dosing information for the first and second infusions is presented as a single statement. | The first and second infusion dosing regimen are not clearly distinguished which may result in wrong dose medication errors. | To improve overall readability and prevent wrong dose errors, we recommend separating out the first and second infusion dosing regimen into two separate statements as follows:<br>• First Infusion: 150 mg intravenous infusion.<br>• Second Infusion: 450 mg intravenous infusion (b) (4) |
| Full Prescribing Information – Section 2 Dosage and Administration | | | |
| 1. | Section 2.3 (Recommended Dosage and Dose Administration) can be improved to more clearly delineate the information presented in this section including Table 1. For example:<br>• The recommended dosing information for the first and second infusions is presented as a single statement.<br>• Amount and volume are presented in same column.<br>• Table 1 does not include the specific diluent (i.e., 0.9 % | This may be revised to better differentiate the information presented in Section 2.3, including Table 1, and to avoid wrong preparation and administration errors. | See Appendix E for recommendations for Section 2 Dosage and Administration (specifically Section 2.3, including Table 1) for the division's consideration. |

| Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | Sodium Chloride Injection, USP) associated with the volume.<br>• Units of dose (mg), volume (mL), and rate (mL/hour) are missing from table headings. | | |
| 2. | The preparation instructions in Section 2.6 (i.e., "Dilute" and "into a") lacks clarity. Additionally, some of the information included under the subheadings in section 2.6 does not align with the subheading titles. | This language may be improved and relocated as needed to prevent wrong preparation medication errors and to increase clarity and appropriate placement of information within the sub-sections. | See Appendix E for recommendations for Section 2 Dosage and Administration (specifically Section 2.6) for the division's consideration. |
| 3. | The following negative warning statements are in Section 2.6:<br>(b) (4) | We have received post-marketing reports in which negative statements are misinterpreted to mean the opposite of the intended meaning because the word, "not" can be overlooked and the warning may be misinterpreted as an affirmative action.[c] | We recommend revising the negative statements to affirmative language such as:<br>"Only use 0.9% Sodium Chloride injection, USP to dilute BRIUMVI."<br>"Administer as an intravenous infusion only"<br>See Appendix E for complete recommendations for Section 2, Dosage and Administration (specifically Section 2.6) for the division's consideration. |

[c] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

| Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| 4. | As currently presented in Section 2.6, the storage statement for after (b) (4) | The intent of the storage statement is unclear. | We defer to OPQ to clarify the correct storage statement for diluted solution. For example:<br>"…store for up to 24 hours in the refrigerator at 2-8°C (36-46°F) and 8 hours at room temperature up to 25°C (77°F)…"<br>or<br>"…store for up to 24 hours in the refrigerator at 2-8°C (36-46°F) or 8 hours at room temperature up to 25°C (77°F)…"<br>Additionally, to increase clarity, we recommend revising the subheading "Storage of Infusion Solution" in Section 2.6 "Use the prepared infusion solution immediately. If not used immediately, store for up to 24 hours in the refrigerator at 2-8°C (36-46°F) and 8 hours at room temperature up to 25°C (77°F), which includes infusion time" to:<br>"Administer immediately after dilution. If diluted solution is not administered immediately, store for up to 24 hours in the refrigerator at 2-8°C (36-46°F) and [or] 8 hours at room temperature up to 25°C (77°F), including infusion time." |
| 5. | In Section 2.6, "USP" is missing for the diluent "Sodium Chloride Injection." | This does not align with USP nomenclature for diluents. | Revise to "0.9% Sodium Chloride Injection" to "0.9% Sodium Chloride Injection, |

| Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | | | USP" wherever it appears in Section 2.6. |
| 6. | In Section 2.6, the statement "After dilution of TRADENAME in the infusion bag, mix by gentle inversion" can be improved to use more direct language (i.e., active voice). | Instructions written in active voice may improve clarity and comprehension. | We recommend revising "after dilution of TRADENAME in the infusion bag, mix by gentle inversion" to "Mix diluted solution by gentle inversion." |

## 5 RECOMMENDATIONS FOR TG THERAPEUTICS, INC.

| Table 3. Identified Issues and Recommendations for TG Therapeutics, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| Container Label and Carton Labeling | | | |
| 1. | The labels and labeling contain the placeholder, "Tradename." | We reference our January 11, 2022, Proprietary Name Conditionally Acceptable Letter informing you that the proprietary name, Briumvi, was found conditionally acceptable. | Revise the labels and labeling to include the conditionally acceptable proprietary name, Briumvi, and use the intend-to-market font, color, etc. |
| 2. | The color contrast of the light gray font color used for the active ingredient and dosage form against the white background appears difficult to read. | Insufficient color contrast may make the text difficult to read. See Final Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety- | Increase the prominence (e.g., use darker or bolder font) of the active ingredient and dosage form taking into account all pertinent factors, including typography, layout, contrast, and other printing features. |

| Table 3. Identified Issues and Recommendations for TG Therapeutics, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | | considerations-container-labels-and-carton-labeling-design-minimize-medication-errors. | |
| Container Label | | | |
| 1. | The format for the expiration date on the container label is not defined. | Clearly define the expiration date to minimize confusion and risk for deteriorated drug medication errors. | Please confirm your expiration date format for your container label will be the same as what is presented on your carton labeling (i.e., DDMMMYYYY). We recommend you use the same format for both the container label and carton labeling. |
| Carton Labeling | | | |
| 1. | The carton labeling instructs "For Intravenous Infusion After Dilution." However, the product requires a specific diluent (0.9% sodium chloride injection, USP) which is not specified on the carton labeling. | To help avoid preparation medication errors associated with using a wrong solution for dilution. | If space permits, we recommend adding the statement "Must be diluted in 0.9% Sodium Chloride Injection, USP prior to use." on the side panel of the carton labeling. |
| 2. | The total product strength/concentration statement "150 mg/ 6 mL" lacks prominence. | Product strength is critical information and should be prominent on the principal display panel per our Final Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety- | To improve prominence and readability, we recommend increasing the prominence (i.e., font size) of the 150 mg/6 mL strength statement, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6). |

| Table 3. Identified Issues and Recommendations for TG Therapeutics, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | | considerations-container-labels-and-carton-labeling-design-minimize-medication-errors | |
| 3. | The net quantity statement can be improved for clarity. | To increase clarity. Additionally, to be consistent with your PI labeling include the package term "single-dose" in the net quantity statement. | Consider revising the net quantity statement "Contains 1 vial" to "Contains one 6 mL single-dose vial." |
| 4. | The Medication Guide statement and location can be improved. | The Medication Guide provides information that is necessary to patients' safe and effective use of the product. Per 21 CFR 208.24(d), the label shall instruct the authorized dispenser to provide a Medication Guide to each patient and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner. | We recommend revising the Medication Guide statement "Attention: Dispense with the enclosed Medication Guide" to "Attention: Dispense the enclosed Medication Guide to each patient." Additionally, we recommend relocating this statement so that it appears prominently on the principal display panel. |

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Briumvi that TG Therapeutics, Inc. submitted on September 28, 2021.

| Table 4. Relevant Product Information for Briumvi | |
|---|---|
| Initial Approval Date | N/A |
| Active Ingredient | ublituximab-wxyz |
| Indication | Relapsing forms of multiple sclerosis, including clinically isolated syndrome (CIS) and relapsing-remitting multiple sclerosis (RRMS) in addition to active secondary progressive disease (SPMS) |
| Route of Administration | Intravenous Infusion |
| Dosage Form | Injection |
| Strength | 150 mg/6 mL (25 mg/mL) |
| Dose and Frequency | The recommended dosage is 150 mg starting dose (Day 1) then 450 mg on Day 15. Administer subsequent infusions (450 mg) every 6 months after the first infusion on Day 1. |
| How Supplied | Supplied as 150 mg in 6 mL (25 mg/mL) single-dose vials in single-count cartons. |
| Storage | This product should be stored refrigerated at 36°F to 46°F (2°C to 8°C) in original carton to protect from light. Do not freeze. Do not shake. Do not use beyond expiration date stamped on carton. Use the diluted solution immediately. If not used immediately, store for up to 24 hours at 2°C to 8°C (36°F to 46°F). (b) (4) |
| Container Closure | (b) (4) colorless glass vials with (b) (4) rubber stoppers that contain a barrier film and sealed with aluminum caps with a plastic button. |

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## APPENDIX F. LABELS AND LABELING

### F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Briumvi labels and labeling submitted by TG Therapeutics, Inc. on September 28, 2021.

- Container label
- Carton labeling
- Medication Guide (Image not shown) available from \\CDSESUB1\evsprod\bla761238\0001\m1\us\ublituximab_medguide_final_clean_26aug2021.pdf
- Prescribing Information (Image not shown) available from \\CDSESUB1\evsprod\bla761238\0001\m1\us\ublituximab-uspi-rms-final-draft_26aug2021.pdf

### F.2 Label and Labeling Images

Container label

(b) (4)

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[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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