CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761238Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761238
PDUFA Goal Date	December 28, 2022
OSE RCM #	2021-1942
Reviewer Name(s)	Donella Fitzgerald, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	December 14, 2022
Subject	Evaluation of Need for a REMS
Established Name	ublituximab
Trade Name	Briumvi
Name of Applicant	TG Therapeutics, Inc.
Therapeutic Class	CD20-directed cytolytic antibody
Formulation(s)	150 mg/6mL single-dose vial
Dosing Regimen	First infusion: 150 mg IV infusion Second infusion: 450 mg IV infusion 2 weeks after 1st dose Subsequent infusions: 450 mg IV infusion every 6 months

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Briumvi (ublituximab) is necessary to ensure the benefits outweigh its risks. TG Therapeutics, Inc. submitted a Biologic Licensing Application (BLA 761238) for ublituximab with the proposed indication for treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The risks associated with ublituximab include serious infections and potential embryofetal toxicity. The Applicant did not submit a proposed REMS or risk management plan with this application.

The safety profile for ublituximab is similar to that of the anti-CD20 monoclonal antibodies (mAbs) approved to treat RMS and the prescribers will likely be specialists experienced with disease modifying RMS therapies and knowledgeable about the serious risks of infection and potential embryofetal toxicity associated with treatment. The risk of serious infections will be included in the Warning and Precautions (Section 5.2) of the ublituximab label. The risk of potential embryofetal toxicity will be included in the Warning and Precautions (Section 5.2) of the label. To obtain additional information regarding potential embryofetal toxicity, DN2 has determined that postmarketing requirements are necessary. A prospective pregnancy exposure registry, pregnancy outcomes study and lactation study will be required postmarketing and is consistent with the requirements for the other approved anti-CD20 therapies. Based on the information available at this time, DRM has determined that a REMS is not needed to ensure the benefits of ublituximab outweigh its risks.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Briumvi (ublituximab) is necessary to ensure the benefits outweigh its risks. TG Therapeutics, Inc. (TGT) submitted a Biologic Licensing Application (BLA) 761238 for ublituximab with the proposed indication for treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. This application is under review in the Division of Neurology 2 (DN2). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Briumvi (ublituximab), a new molecular entity[a], is a recombinant immunoglobulin (Ig) G1 chimeric monoclonal antibody (mAb) proposed for treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

disease, in adults. Briumvi binds to the cell surface antigen, CD20, resulting in antibody-dependent cellular cytolysis, cellular phagocytosis and complement-mediated lysis of B cells that contribute to tissue damage in multiple sclerosis (MS). It is proposed as a 150 mg/6 mL concentrate for solution for intravenous (IV) infusion to be supplied in a single-dose glass vial. Briumvi is to be taken chronically.[b] The dosing schedule is as follows: First infusion- 150 mg, second infusion- 450 mg 2 weeks after first dose, subsequent infusions- 450 mg every 6 months. Briumvi is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761238 relevant to this review:

- **09/28/2021:** BLA 761238 submission for treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults, received.
- **03/08/2022:** DN2 issued a Clinical Information Request (IR) for serious adverse event (SAE) narratives for all subjects in the clinical trials.
- **03/31/2022:** Applicant's initial response to the 3/8/22 IR received. SAE narratives for subjects who received ublituximab were provided.
- **04/05/2022:** Applicant's follow-up response to the 3/8/22 IR received. SAE narratives for subjects who received teriflunomide (comparator) were provided.
- **05/27/2022:** Major amendment acknowledgment letter sent to the applicant; PDUFA goal date extended by 3 months to allow for review of the IR responses submitted to the Agency on 3/31/22 and 4/5/22.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

MS is a chronic neurodegenerative disorder of the central nervous system with variable clinical and pathologic features.[c] Inflammation, demyelination, and axon degeneration are the major pathologic mechanisms that cause the clinical manifestations, which commonly include sensory disturbances, visual loss, motor weakness, diplopia, gait disturbance, balance problems, and other symptoms. The cause of MS remains unknown. It is believed that a combination of genetic factors, immune system

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

abnormalities, and environmental factors triggers the disease. The core MS phenotypes are relapsing-remitting and progressive disease. The pattern and course of MS is further categorized into several clinical subtypes: clinically isolated syndrome, relapsing-remitting, secondary progressive and primary progressive.

It is estimated that nearly one million people in the United States are currently living with MS.[1,d] Most people who develop MS are between the ages of 20 and 50, with women having three times greater risk of developing MS than males. Though disease severity is variable, it is estimated that MS can shorten one's life expectancy by approximately seven years on average.[2]

3.2. Description of Current Treatment Options

A number of disease modifying therapies have been approved in the US to treat RMS and include administration by subcutaneous, oral, and intravenous routes. Monoclonal antibodies (mAb) that work by targeting the CD20 antigen on B cells (anti-CD20), as ublituximab does, are the most recent and innovative treatment options, as B cell depleting therapy has shown to be highly effective against RMS.[3] Ocrelizumab, approved in 2017, and ofatumumab, approved in 2009 are both widely used anti-CD20 MS treatment options. In addition to the anti-CD20 therapies, two other mAbs are approved for treatment of RMS: natalizumab and alemtuzumab. Both of these products are approved with a REMS to mitigate serious risks. Natalizumab has a REMS to mitigate progressive multifocal leukoencephalopathy and alemtuzumab has a REMS to mitigate autoimmune conditions, infusion reactions, stroke and malignancies. An additional agent, teriflunomide, a pyrimidine synthesis inhibitor, was approved to treat RMS in 2012. A summary of the FDA approved treatments for RMS is included in Table 1 below:

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Table 1: Summary of Treatment Options Relevant to Proposed Indication

Product Trade Name (Generic) Year of Approval	MOA	Indication	Administration	Important Safety and Tolerability Issues	Risk Management Approaches/ Boxed Warning, Medication Guide (MG)
FDA Approved Treatments for RMS					
Ocrevus (ocrelizumab) 2017	Anti-CD20 mAb	Relapsing and primary progressive MS	IV injection	Infusion reactions, infections, reduced immunoglobins, malignancies, fetal harm	MG
Aubagio (teriflunomide) 2012	Pyrimidine synthesis inhibitor	RMS	Oral tablet	Hepatotoxicity, embryofetal toxicity	Boxed warning, MG
Kesimpta (ofatumumab) 2009	Anti-CD20 mAb	RMS	SC injection	Infections, injection reactions, reduced immunoglobins, fetal risk	MG
Tysabri (natalizumab) 2004	Integrin receptor antagonist	RMS, Crohn's disease	IV infusion	PML, hypersensitivity reactions, fetal harm	REMS, boxed warning, MG
Lemtrada (alemtuzumab) 2001	CD52 cytolytic mAb	RMS	IV infusion	autoimmune conditions, infusion reactions, stroke, malignancies, fetal harm	REMS, boxed warning, MG
Other treatments: massage, acupuncture, evening primrose oil, pulsed electromagnetic field therapy, cooling therapy, reflexology					

Despite improvements in the available RMS therapies, patients continue to experience disease relapses and progression. As RMS is a chronic disease which impacts patient's quality of life, unmet treatment goals continue to exist for patients with MS.

4. Benefit Assessment

The pivotal trials (RMS301 [NCT03277261], RMS302 [NCT03277248]) supporting this application consisted of two 120-week, Phase 3, randomized, multicenter, double-blind, double-dummy, active-controlled studies identical in design. The studies were primarily designed to assess the annualized relapse rate (ARR) of ublituximab/oral placebo compared to teriflunomide/IV placebo in subjects with RMS. The ARR is defined as the ratio of the sum of all subjects' relapse counts divided by the sum of all subjects' treatment duration in years. In both studies subjects were screened up to 4 weeks before the first dosing date of study medication. Qualified subjects were then randomized in a 1:1 ratio to receive either ublituximab/oral placebo or teriflunomide/IV placebo per the below dosing regimen:

Table 2: RMS301 and RMS302 Dosing Regimen

	Week 1 Day 1	Week 3 Day 15	Week 24	Week 48	Week 72	Week 96
Ublituximab plus oral placebo	UTX (150 mg/4 h)	UTX (450 mg/1 h)	UTX (450 mg/1 h)	UTX (450 mg/1 h)	UTX (450 mg/1 h)	-
	Oral placebo QD[a] from Week 1 Day 1 until the last day of Week 95					
Teriflunomide plus IV placebo	Teriflunomide (14 mg) QD[a] from Week 1 Day 1 until the last day of Week 95					
	IV placebo	IV placebo	IV placebo	IV placebo	IV placebo	-

Abbreviations: IV, intravenous; QD, once daily; UTX, ublituximab.
[a] May have been taken in the morning daily. Alternative dosing times were allowed if necessary.

Upon cessation of study treatment, the subjects were followed for another 20 weeks to enable teriflunomide elimination monitoring.

Both studies demonstrated a significant ARR reduction with ublituximab compared to teriflunomide. Study RMS301 consisted of 548 subjects (273 ublituximab, 275 placebo) and showed a 59.4% reduction in ARR with ublituximab use (UTX 0.09 versus placebo 0.23, $p<0.0001$). Study RM302 consisted of 545 subjects (272 ublituximab, 273 placebo) and showed a 49.1% reduction in ARR with ublituximab use (UTX 0.11 versus placebo 0.22, $p=0.0022$). The medical officer concluded that the clinical studies provided substantial evidence that treatment of RMS with ublituximab provides clinically meaningful benefit (i.e., reduction of relapses).[4,e]

5. Risk Assessment & Safe-Use Conditions

The primary safety analysis consists of data from 545 subjects treated with ublituximab during the Phase 3 clinical trials (RMS301, RMS302). Supportive safety data from the long-term extension trial (RMS303, [NCT04130997]) and Phase 2 dose finding study (RMS201E, [NCT03381170]) is also included.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

As of the October 29, 2021 data cut-off date, three deaths (0.6% subjects; [encephalitis, pneumonia, salpingitis]) were reported in the Phase 3 studies, ten (1.6% subjects; [COVID-19]) in the long-term extension trial (RMS303) and one (2.2% subjects; [COVID-19 pneumonia]) in the Phase 2 dose finding study. All of the deaths were reported in ublituximab treated patients. The medical officer noted that, excluding COVID-19 related deaths, the ublituximab subject deaths is quantitatively similar to those seen in the other anti-CD20 (ocrelizumab, ofatumumab) clinical development programs, however, the severity and nature of the deaths from infections is unique to ublituximab.[5]

Serious adverse events (SAEs) occurring in more than one subject during the Phase 3 trials occurred in 59 (10.8%) subjects for ublituximab and 40 (7.3%) for teriflunomide. Pneumonia, including COVID-19 pneumonia, was the most frequently reported SAE, occurring in 1.6% of the subjects reporting SAEs. The below table summarizes all the SAEs occurring in >1 subject in either treatment group across the double-blind period of the two Phase 3 trials:

Table 3: SAEs occurring in >1 subject in either treatment group across the double-blind period of the two Phase 3 trials

	Ublituximab (N = 545)	Teriflunomide (N = 548)
Total Subjects with any SAE	59 (10.8)	40 (7.3)
Pneumonia	5 (0.9)	2 (0.4)
COVID-19 pneumonia	4 (0.7)	2 (0.4)
Neurological symptom	1 (0.2)	4 (0.7)
Acute sinusitis	3 (0.6)	0 (0.0)
Muscular weakness	1 (0.2)	2 (0.4)
Pyelonephritis acute	0 (0.0)	3 (0.5)
Appendicitis	2 (0.4)	0 (0.0)
Central nervous system enteroviral infection	2 (0.4)	0 (0.0)
Complicated appendicitis	1 (0.2)	1 (0.2)
Concussion	1 (0.2)	1 (0.2)
Epilepsy	0 (0.0)	2 (0.4)
Urinary tract infection	0 (0.0)	2 (0.4)

5.1. Serious Infections

In the phase 3 studies, treatment emergent adverse events (TEAEs) of Grade ≥3 serious infections were reported in more subjects in the ublituximab groups compared to subjects in the teriflunomide groups (3.7% versus 1.8%). The most common Grade ≥3 serious infections were pneumonia (ublituximab: 0.7%; teriflunomide: 0.2%) and COVID-19 pneumonia (ublituximab: 0.7%; teriflunomide: 0.2%). Serious infections that led to discontinuation of ublituximab included central nervous system enteroviral infection (two subjects), pulmonary tuberculosis, and meningoencephalitis viral.

For three subjects treated with ublituximab, the serious infections (encephalitis, pneumonia, salpingitis) were fatal. The patient who developed encephalitis was a 32-year-old female hospitalized on (b) (6) (day 405) and expired (b) (6) (day 451). Her last infusion of ublituximab was on (b) (6). Per the applicant, her death was not considered related to ublituximab, but associated with a past medical history of Grade 3 measles.

The patient who died of pneumonia was a 36-year-old male who was hospitalized and died from pneumonia on (b) (6). The last date of his ublituximab IV infusion was on (b) (6), and the last reported date of oral placebo intake was on (b) (6). The applicant concluded that the event of pneumonia was considered possibly related to ublituximab.

The last death related to serious infection occurred in a 22-year-old female who experienced an event of salpingitis on (b) (6) after undergoing a tubotomy and salpingostomatoplasty in (b) (6) for an ectopic pregnancy. The last date of ublituximab infusion was on (b) (6). The subject died on (b) (6). Per the applicant, the event of salpingitis was considered not related to ublituximab.

The medical officer disagrees with the applicant regarding the association of ublituximab with the three deaths. She concluded that immunosuppression from ublituximab may likely have contributed to the development or severity of the infections in the subjects. The medical officer noted that serious infections have also been reported with other anti-CD20 therapies approved for RMS, and the relative risk compared to teriflunomide appears similar to that observed in controlled trials for ublituximab. She concluded that "the observed clinical benefit associated with ublituximab is thought to outweigh this risk."[6]

Healthcare providers will likely be familiar with managing the risk of serious infections with RMS treatment, as an increased risk of infections, including serious and fatal bacterial, fungal, and new or reactivated viral infections, has been observed with other anti-CD20 B-cell depleting therapies (ocrelizumab, ofatumumab). Other approved treatments for RMS, such as natalizumab and alemtuzumab also include an infection risk in their prescribing information. The risk of serious infections will be included in the Warning and Precautions (Section 5.2) of the ublituximab label. The draft language currently states that "serious, including life-threatening and fatal infections, have occurred." Additionally, the applicant proposed a Medication Guide that also includes language informing patients that ublituximab increases their risk of getting infections.

5.2. Embryofetal Toxicity

Nonclinical Findings

The applicant stated that based on findings from animal studies, ublituximab may cause fetal harm, and based on the mechanism of action, may cause infant B-cell depletion. In a pre- and post-natal development study, pregnant cynomolgus monkeys were administered weekly IV doses of 30 mg/kg ublituximab during the first, second or third trimester of pregnancy. Ublituximab elicited a profound immunogenic response in pregnant monkeys, resulting in maternal moribundity (10/34) and fetal loss

(12/24).[7] The study was terminated early; 3rd trimester enrollment was incomplete. No fetal abnormalities were found in the infants treated during the 1st trimester, but for fetuses exposed to ublituximab during the 2nd trimester, findings included musculoskeletal and central nervous system-related abnormalities. The applicant stated that the dose of 30 mg/kg in the pregnant monkeys resulted in exposures 26 times the exposure in human subjects with RMS at the recommended labeling dose of 450 mg. However, the pharmaco-toxicology reviewer concluded that the reported exposure level is likely inaccurate and that a no observed adverse effect level (NOAEL) and safety margin cannot be determined due to only one dose level being studied.[8]

Clinical Findings

In the clinical trials there were twelve human pregnancies reported. Nine pregnancies were reported in subjects receiving ublituximab. Of the nine were 3 elective abortions, 4 full-term healthy babies and 2 unknown outcomes. There were also 3 pregnancies reported in partners of subjects receiving ublituximab. This included 1 elective abortion, 1 unknown outcome and 1 full-term healthy baby. The Division of Pediatrics and Maternal Health (DPMH) was consulted by DN2 to provide feedback on labeling for potential fetal harm. DPMH recommended a Warning and Precaution for embryofetal toxicity and stated that "*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*."[9] In their consult, DPMH recommended pregnancy testing prior to initiation of therapy and the use of effective contraception by females of reproductive potential during therapy and for 6 months after the last dose. The consult stated that the contraception recommendations would help to maintain consistency with the labeling for approved anti-CD20 therapies (ocrelizumab, ofatumumab). Lastly, DPMH recommended that the applicant be required to conduct a prospective pregnancy registry cohort analysis and additional pregnancy outcomes study as postmarketing requirements.

At the time of this review, labeling is ongoing. The current draft label includes language recommending pregnancy testing under Section 2.2 Assessment and Premedication. Embryofetal toxicity is included under Warnings and Precautions (Section 5.3) and pregnancy under Use in Specific Populations (Section 8.1). Additional recommendations for pregnancy testing and contraception for females and males of reproductive potential are listed in Section 8.3 (Use in Specific Populations). The Patient Counseling Information (Section 17) also includes language regarding potential fetal risk and the need for contraception. Similar language is included in the Medication Guide proposed by the Applicant.

6. Expected Postmarket Use

Ublituximab is expected to be prescribed primarily in an outpatient setting to be administered by a healthcare professional in an infusion center. In most cases it will be prescribed by specialists, with neurologists being the most likely prescribers. These clinicians will likely have experience with RMS therapies, including anti-CD20 mAbs, and are knowledgeable about the risks associated with treatment.

Healthcare providers will likely counsel patients at the point of care regarding the observed risk of serious infection and potential risk of embryofetal toxicity associated with ublituximab treatment. Additionally, a MG that includes information regarding these risks will be available for patients. Providers will likely be able to take necessary actions to lower patient's risk of serious infections, such as delaying ublituximab treatment in the presence of an active infection and avoiding vaccination with live-attenuated or live vaccines. Per the draft label, patients should be counseled regarding the potential risk of embryofetal toxicity and advised to use contraception during and for at least 6 months after stopping ublituximab treatment. To obtain additional information regarding the risks of embryofetal toxicity, DN2 has determined that postmarketing requirements are necessary. A prospective pregnancy exposure registry, pregnancy outcomes study and lactation study will be required postmarketing and is consistent with the requirements for the other approved anti-CD20 mAbs.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for ublituximab beyond routine pharmacovigilance and labeling. They stated that the overall risk profile of ublituximab is manageable and that guidance to manage risks with supportive care, treatment interruption or permanent discontinuation of ublituximab are provided in the label. The applicant also proposes a Medication Guide to communicate risks of ublituximab treatment to patients.

8. Discussion of Need for a REMS

Based on the efficacy and safety information currently available, the Clinical Reviewer recommends approval of ublituximab for the treatment of RMS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.[10]

MS is a highly debilitating neurological condition affecting approximately one million people in the U.S. and is characterized by sensory disturbances, visual difficulties, muscle weakness, and gait abnormalities that can ultimately result in a chronic disabled state. There is no cure for MS but a number of disease modifying therapies, including two anti-CD20 mAbs, have been approved for treatment. If approved, ublituximab would add an additional therapeutic option for the treatment of MS. The benefits of treatment with ublituximab were demonstrated by meeting the primary endpoint of significant reduction in the annualized relapse rate for RMS patients as compared to teriflunomide in the Phase 3 trials.

The safety profile for ublituximab is similar to that of the anti-CD20 mAbs approved to treat RMS. Treatment-emergent serious infections, some of which were fatal, were observed during the clinical trials. An increased risk of infections, including serious and fatal, were also observed during and following completion of treatment with other anti-CD20 B-cell depleting therapies (ocrelizumab, ofatumumab), as well as other approved RMS therapies such as teriflunomide, natalizumab and

alemtuzumab. The proposed label for ublituximab includes a Warning and Precaution for serious infections and recommends treatment delay for patients with active infection. Additionally, it recommends against vaccination with live-attenuated or live vaccines during treatment with ublituximab.

Embryofetal toxicity was identified as a potential risk needing further evaluation as no definitive conclusion can be made from the available data. Data from the clinical trials did not reveal any congenital malformations in the exposed human pregnancies, although non-clinical studies in cynomolgus primates resulted in maternal toxicity and death, as well as fetal loss and malformation. The pharmaco-toxicology reviewer stated that a no observed adverse effect level and safety margin cannot be determined due to only one dose level being studied in the primate study. DPMH recommended a Warning and Precaution for embryofetal toxicity based on the non-clinical data. They also recommended language regarding pregnancy testing and contraception based on the risks of B-cell depletion and potential embryofetal toxicity. Prescribers will likely be familiar with this potential risk as labeling for ocrelizumab, ofatumumab, teriflunomide, natalizumab and alemtuzumab all include language regarding possible fetal harm. None of the aforementioned therapies include a REMS for embryofetal toxicity, but teriflunomide does include a boxed warning. Due to the limited data, DN2 concluded that ublituximab does not warrant a boxed warning for embryofetal toxicity but will require postmarketing studies that include: a prospective pregnancy exposure registry, pregnancy outcomes study and a lactation study. Based on the information available at this time, DRM has concluded that risk mitigation beyond professional labeling is not necessary for the potential risk of embryofetal toxicity or serious infections. If additional information becomes available that changes the risk-benefit analysis, the need for a REMS may be re-evaluated.

DRM and DN2 agree that based upon available clinical information, a REMS is not necessary at this time to ensure the benefits outweigh the risks of ublituximab for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

9. Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks. In general, healthcare providers who treat RMS are familiar with the risks of serious infections and embryofetal toxicity and the importance of patient counseling regarding these risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

[1] National Multiple Sclerosis Society 2022. Landmark Study Estimates Nearly 1 Million in the U.S. Have Multiple Sclerosis | National Multiple Sclerosis Society (nationalmssociety.org).

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[3] Hauser SL, Cree BAC. Treatment of Multiple Sclerosis: A Review. *Am J Med*. 2020;133(12):1380-1390.

[4] Baldarassi, L. Division of Neurology 2. Draft Clinical review for ublituximab, BLA 761238, December 9, 2022.

[5] Baldarassi, L. Division of Neurology 2. Internal midcycle clinical presentation for ublituximab, BLA 761238, February 28, 2022.

[6] Baldarassi, L. Division of Neurology 2. Draft Clinical review for ublituximab, BLA 761238, December 9, 2022

[7] Wilcox, B. Division of Neurology 2. Non-clinical mid-cycle meeting presentation for ublituximab, BLA 761238.

[8] Division of Neurology 2. Pharmacology/Toxicology late cycle meeting presentation for ublituximab, BLA 761238.

[9] Roca, C. Division of Pediatric and Maternal Health. Consult review for ublituximab, BLA 761238, August 29, 2022.

[10] Baldarassi, L. Division of Neurology 2. Draft Clinical review for ublituximab, BLA 761238, December 9, 2022

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