CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761238Orig1s000

SUMMARY REVIEW

Summary Review

Date	December 28, 2022
From	Paul R. Lee, MD, PhD, Deputy Director, Division of Neurology 2 Billy Dunn, MD, Director, Office of Neuroscience
Subject	Summary Review
BLA #	761238
Applicant	TG Therapeutics
Date of Submission	09/28/2021
PDUFA Goal Date	12/28/2022 extended from 09/28/2022
Proprietary Name	Briumvi
Established or Proper Name	ublituximab-xiiy
Dosage Form(s)	150 mg/6 mL (25 mg/mL) single-dose vial
Applicant Proposed Indication(s)/Population(s)	Adults with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.
Applicant Proposed Dosing Regimen(s)	First infusion: 150 mg intravenous (IV) infusion Second infusion (2 weeks later): 450 mg IV infusion Subsequent infusions (every 6 months): 450 mg IV infusion
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adults with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.
Recommended Dosing Regimen(s) (if applicable)	Same as proposed

Benefit-Risk Integrated Assessment

Briumvi (ublituximab-xiiy) is a glycoengineered murine/human chimeric anti-CD20 monoclonal antibody that targets an epitope of the B-lymphocyte antigen CD20 expressed on the cell membranes of lymphocytes. After binding to CD20, ublituximab-xiiy induces B-cell destruction primarily by antibody-dependent cell-mediated cytotoxicity. Ublituximab-xiiy is proposed as a treatment for relapsing forms of multiple sclerosis (MS). There are at present two anti-CD20 monoclonal antibody therapies approved to treat relapsing forms of MS. Ocrevus (ocrelizumab) is a humanized murine/human chimeric anti-CD20 monoclonal antibody that is approved for the treatment of the relapsing forms of MS and is approved additionally for the treatment of the primary progressive form of MS. Kesimpta (ofatumumab) is a fully-human anti-CD20 monoclonal antibody approved for the treatment of relapsing forms of MS. Rituxan (rituximab) is a chimeric murine/human anti-CD20 monoclonal antibody which is approved to treat several malignancies and rheumatologic autoimmune diseases; rituximab is sometimes used to treat MS but has not been demonstrated to be safe and effective for the treatment of MS.

Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (secondary progressive MS with relapses), are phenotypes of the chronic and disabling central nervous system disease of apparent autoimmune etiology termed "multiple sclerosis." In the relapsing forms of MS, subjects experience episodes of focal neurological deficits and disseminated lesions of demyelination within the central nervous system. Symptoms of relapsing forms of MS commonly include recurrent paroxysms of diminished sensory or motor function that can be temporarily or permanently disabling. Many, but not all, subjects with relapsing forms of MS experience some degree of persistent disability that may gradually worsen over years. Over twenty unique therapies have been approved for the treatment of relapsing forms of MS, and all of these approved therapies share a basic common feature of modifying the immune response. The mechanism of action of anti-CD20 therapies in the treatment of relapsing forms of MS is unknown but presumably is linked to depletion of B-cells and immunosuppression.

The applicant presents the results from two adequate and well-controlled Phase 3 clinical trials, Studies TG1101-RMS301 and TG1101-RMS302 (Studies RMS301 and RMS302 hereafter) as the basis of an application to support a claim of safety and efficacy for ublituximab-xiiy in the treatment of relapsing forms of MS. Studies RMS301 and RMS302 were both randomized, double-blind, double-dummy, active-controlled trials that compared intravenous ublituximab to teriflunomide. The two studies were identical in design with the same primary efficacy outcome measure, the annualized relapse rate (ARR), as well as the same hierarchical analysis of secondary efficacy outcome measures as follows: the number of gadolinium-enhancing T1 lesions, the number of new or enlarging T2 lesions, a pooled analysis of 3-month confirmed disability worsening from both studies, the proportion of subjects with no evidence of disease activity from Week 24 to Week 96, the proportion of subjects reaching impaired symbol digit modality test from Baseline to Week 96, and the percentage change in brain volume from Baseline to Week 96.

In both studies, treatment with ublituximab-xiiy resulted in statistically significant reductions in ARR compared to treatment with teriflunomide. These significant results in Studies RMS301 and RMS302 were achieved relative to an active comparator, teriflunomide, a therapy itself approved for the treatment of relapsing forms of MS based upon a significant treatment effect on relapse frequency in placebo-controlled studies. With respect to the primary efficacy outcome finding, in Study RMS301, subjects treated with ublituximab-xiiy had a significant ($p<0.0001$) relative reduction of 59% in ARR as compared to teriflunomide-treated subjects' ARR. In Study RMS302, the relative reduction in ARR was 49% in ublituximab-xiiy treatment relative to teriflunomide treatment, and this finding also was statistically significant ($p=0.0022$). There were significant findings in gadolinium-enhancing T1 and T2 lesion outcomes for ublituximab-xiiy that provide further evidence to support the significant treatment effect observed on ARR. A comparison of pooled data from Studies RMS301 and RMS302 failed to demonstrate a significant treatment effect on the 3-month risk of confirmed disability worsening (16% relative reduction, $p=0.5099$) with ublituximab-xiiy as compared to teriflunomide.

Anti-CD20 therapies like ublituximab-xiiy reduce the number of B-cells available to prevent and combat infection and therefore are potent immune suppressants. The safety findings for ublituximab-xiiy in subjects with relapsing forms of MS were similar to reported safety outcomes with other anti-CD20 therapies in MS. Infections were among the most common treatment-emergent adverse events (5.5% and 4.4%, in Studies RMS301 and RMS302, respectively) observed in association with ublituximab-xiiy treatment. The most common serious adverse event associated with ublituximab-xiiy was an increased risk of infections; serious infections occurred in 5.5% of subjects treated with ublituximab as compared to 2.2% of subjects treated with teriflunomide. Serious, potentially fatal, opportunistic infections such as progressive multifocal leukoencephalopathy (PML) have been reported in subjects treated with other anti-CD20 therapies; there were no cases of PML in subjects with MS treated in these trials, but the potential for PML infection exists with ublituximab-xiiy. There were three subjects who died from infections in the controlled trials who were randomized to ublituximab-xiiy. However, frequency of infections observed in Studies RMS301 and RMS 302 were consistent with findings of other anti-CD20 therapies, and this potentially fatal risk can be mitigated through labeling warnings as it is with other approved anti-CD20 monoclonal antibody therapies. Infusion-related reactions occurred in approximately half (47.7%) of subjects treated with Briumvi and were considered serious in 0.7% of subjects. Infusion-related reactions are common with anti-CD20 therapies delivered via the intravenous route and can be mitigated with pre-treatment regimens and labeling warnings. A fraction of subjects treated with ublituximab-xiiy had a sustained, progressive decline in immunoglobulins M and G which could predispose to possible infection risk; this reduction in antibodies is a consequence of all anti-CD20 therapies and worsens with chronic exposure. Labeling warnings regarding monitoring serum immunoglobulins, and a postmarketing requirement will explore this immunoglobulin safety issue as it relates to a potential but not yet fully-characterized associated risk of serious infections. Ublituximab-xiiy exposure in primates appeared to have direct effects on fetal development; pregnancy testing prior to administration and a warning regarding potential fetal harm are needed to mitigate this potentially serious risk given that the population exposed to ublituximab-xiiy will be disproportionately women of childbearing potential due to the established demographics of MS.

The overall benefit-risk profile of ublituximab-xiiy supports approval. The labeling for ublituximab-xiiy will include a warning regarding infection risk, including the known risk of serious potentially fatal infections identified with the use of ublituximab-xiiy, a warning of potential fetal harm, and a warning of reduced immunoglobulins with chronic use.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (SPMS with relapses), are phenotypes of the chronic and potentially disabling central nervous system disease known as MS, a disease of apparent autoimmune etiology which in its relapsing form is characterized by episodes of worsening focal neurological deficits and disseminated lesions representing demyelination. • The usual age of onset of relapsing forms of MS is 20 to 50 years old. Symptoms commonly include recurrent paroxysms of diminished sensory or motor function that can be disabling and usually resolve within one month. Over time, many, but not all, subjects with relapsing forms of MS experience some degree of persistent disability that may gradually worsen over years. Some subjects may have a relatively benign manifestation with few discrete relapse events; others may become severely disabled after only a few years. There are no reliable biomarkers or predictors of outcome.	Relapsing forms of MS are serious and disabling. The defining symptom of relapsing forms of MS are paroxysms of focal neurological deficits termed "relapses" which can be disabling and reduce quality of life.
Current Treatment Options	• There are over twenty unique therapies approved to treat relapsing forms of MS. All of these therapies reduce subject relapse rates, and many include disability progression outcomes in their labeling.	All therapies approved for the treatment of relapsing forms of MS reduce the frequency of relapses and some of these therapies also reduce accumulation of disability.
Benefit	• The annualized relapse rates in subjects treated with ublituximab-xiiy were 0.076 and 0.188, vs. 0.091 and 0.178 for teriflunomide-treated subjects. Based on the results of Studies RMS301 and RMS302, the percent reductions in relapse rate associated with Briumvi treatment relative to teriflunomide treatment were 59% and 49%, respectively.	Two adequate and well-controlled trials of Briumvi provided substantial evidence of efficacy by demonstrating a significantly reduced likelihood (approximately half) of experiencing a relapse relative to an active comparator which is approved to treat relapsing forms of MS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Ublituximab-xiiy treatment was not associated with a significant effect on confirmed disability as compared to teriflunomide.	Unlike other anti-CD20 therapies approved to treat MS, the pooled results from two adequate and well-controlled trials did not provide evidence that ublituximab-xiiy significantly reduced the likelihood of accumulation of disability in subjects with relapsing forms of MS relative to an active comparator. Teriflunomide, the active comparator in this trial, has demonstrated a significant reduction is disability worsening in adequate and well-controlled trials. These clinical trials comparing ublituximab-xiiy to teriflunomide were not designed to demonstrate non-inferiority on disability treatment.
Risk and Risk Management	• Ublituximab-xiiy, a monoclonal antibody targeting CD20, causes immune suppression by selectively reducing the number of B-cells and the safety database from the ublituximab-xiiy program yields a safety profile that is similar and consistent with these other therapies which cause immune suppression via reduction in B-cell counts. • Three subjects in the ublituximab-xiiy treatment arms died from infections. There were no deaths in the teriflunomide treatment arms of the Phase 3 trials. • The most common treatment-emergent adverse events reported in subjects treated with ublituximab-xiiy were headache (34.3%), nasopharyngitis (18.3%), pyrexia (13.9%), and nausea (10.6%). • Infusion-related reactions occurred in 47.7% of ublituximab-xiiy subjects. The majority of injection-related reactions associated	The safety data from the ublituximab-xiiy MS development program support approval and are consistent with other anti-CD20 therapies approved to treat MS. Deaths due to anti-CD20 therapy immunosuppression have been reported with all anti-CD20 therapies. Most adverse events associated with ublituximab-xiiy were treatable, not medically serious, or reversible upon discontinuation. Infusion-related reactions occurred in nearly half of subjects infused with ublituximab-xiiy but almost all reactions were mild and required no treatment. Monitoring for infusion-related reactions should be conducted in the first two infusions and continued

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with ublituximab-xiiy occurred during the first two infusions, were mild, and did not require treatment. Less than 1% of infusion-related reactions were serious. • There were three deaths reported in subjects treated with ublituximab-xiiy in the Phase 3 clinical trials. All three deaths were infection-related. • Serious adverse events associated with treatment occurred in approximately 11% of subjects treated with ublituximab-xiiy and approximately 7% of subjects treated with the active comparator, teriflunomide. The most common serious adverse events in both treatment arms of both Phase 3 trials were infections. The most common infection in subjects treated with ublituximab-xiiy was pneumonia (1.7%). Hepatitis reactivation occurred in several subjects treated with ublituximab-xiiy. There were no cases of progressive multifocal leukoencephalopathy (PML) observed in the ublituximab-xiiy development program. • In Studies RMS301 and RMS302, the rate of adverse events leading to ublituximab-xiiy discontinuation were 6.6% and 1.8% as compared to 0.7% and 0.7% in the teriflunomide treatment arms. The most common reason for discontinuation of ublituximab-xiiy was infections (categorically) and enteroviral meningitis (0.7%), specifically. • Nonclinical studies in primates revealed fetal malformations and suggested ublituximab-xiiy may cause toxic effects on fetal tissues.	beyond these initial infusions only if subjects experience an infusion-related reaction. Immunosuppression using anti-CD20 therapies selectively reduces B-cells and confers unavoidable increased risk of any infection. Serious and potentially fatal infections are rare complications of immune suppression and labeling for most therapies used to treat MS include warnings regarding the risks of serious and fatal infections associated with treatment. The labeling for Briumvi will indicate a risk of hepatitis B reactivation which is an established risk of anti-CD20 therapies. The labeling will also indicate a risk of PML even though no cases of this serious infection was observed in clinical trials because of the known risk of PML established for other anti-CD20 monoclonal antibody therapies. Labeling will warn that animal studies suggested risk of fetal harm and advise continuous use of effective contraception. Pregnancy testing will be recommended before ublituximab-xiiy administration. There will be a required postmarketing pregnancy registry and a required postmarketing pregnancy outcomes study as well as enhanced pharmacovigilance for fetal complications.

1. Background

This application contains data in support of the safety and effectiveness of Briumvi (ublituximab-xiiy) for the treatment of relapsing forms of multiple sclerosis (MS), a glycoengineered chimeric murine/human anti-CD20 monoclonal antibody that selectively targets an epitope of the CD20 molecule on the cell membrane of B-cells. Ublituximab-xiiy is administered intravenously as two different doses separated by two weeks (first infusion: 150 mg, second infusion administered 2 weeks later: 450 mg) then continued at 450 mg every six months as a maintenance dose. This application was submitted as a new Biologics License Application (BLA) for Briumvi which is not approved or marketed elsewhere at the present time.

Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and secondary progressive MS with relapses (active secondary progressive disease), are related phenotypes of a chronic and disabling central nervous system disease of apparent autoimmune etiology characterized by episodes of worsening focal neurological deficits and disseminated lesions of demyelination. Subjects diagnosed with relapsing forms of MS are typically White women between 20 to 50 years of age. Symptoms of relapsing forms of MS commonly include recurrent paroxysms of diminished sensory or motor function that can be disabling and usually resolve within one month. As disease duration increases, many, but not all, subjects with relapsing disease experience some degree of persistent disability that may gradually worsen over years as a result of incomplete recovery of the disability that resulted from MS relapses. In some subjects, disability may accrue progressively with clear independence from acutely disabling relapse events, a process termed secondary progressive disease.

There is no widely accepted biomarker to assess disease status in subjects with relapsing forms of MS. The diagnosis of relapsing forms of MS relies on clinical criteria, and the ongoing evaluation of subjects with MS is reliant on clinical investigation. To support an indication for the treatment of relapsing forms of MS, clinical trials should demonstrate that a therapy is associated with a significant, clinically meaningful decrease in the frequency of MS-associated relapses, typically measured as an annualized relapse rate (ARR). Some therapies approved for the treatment of relapsing forms of MS, including another anti-CD20 therapy, have also demonstrated an additional significant reduction of the accrual of disability over three-month or six-month observational periods.

In 2017, Ocrevus (ocrelizumab) was the first anti-CD20 therapy approved for the treatment of relapsing forms of MS (as well the first approved therapy for primary progressive MS) in adults. Ocrelizumab is a humanized murine anti-CD20 monoclonal antibody and is administered as an initial 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion, with subsequent maintenance doses of 600 mg intravenously infused over 2-3.5 hours every 6 months. Rituxan (rituximab), an anti-CD20 chimeric murine-human monoclonal antibody, became the first anti-CD20 monoclonal antibody therapy approved for any indication in 1997. Rituximab is not indicated for the treatment of MS but is used to treat MS and other neuroimmune diseases on an "off-label" basis. Rituximab's relatively higher antigenicity is a consideration in its safety and efficacy. Kesimpta (ofatumumab) is a fully human monoclonal antibody administered subcutaneously that was approved for the treatment of relapsing forms of MS in 2020. Briumvi is intended for the treatment of relapsing forms of MS and would provide a third effective therapy for this indication in this class, and Briumvi would represent an option for individuals who do not tolerate other anti-CD20 therapies because it is a different monoclonal antibody and targets a different epitope than other approved treatments. Briumvi has a shorter duration of infusion during maintenance therapy (1 hour) than the other available intravenous therapies which would reduce the time spent in infusion centers and may be an appealing treatment difference for some subjects.

The CD20 antigen is a transmembrane calcium channel that is expressed on the surfaces of B-cells beginning in the late pre-B-cell stage of maturation through the fully matured memory B-cell. Administration of anti-CD20 therapies such as ublituximab-xiiy reduces B-cell counts in serum via B-cell lysis by complement-dependent cytotoxicity (CDC) and by antibody-dependent cell-mediated cytotoxicity (ADCC). The precise mechanism by which ublituximab-xiiy exerts its therapeutic effects in MS is not known, but immune suppression by a variety of treatments that deplete B-cells, including the two other approved anti-CD20 monoclonal antibody therapies, ocrelizumab and ofatumumab, reduces relapses and, in some but not all B-cell targeting therapies, prevents the accumulation of significant disability in subjects with various forms of MS.

The applicant presents results from two adequate and well-controlled Phase 3 clinical trials as the basis of support for the effectiveness of ublituximab-xiiy for the treatment of relapsing forms of MS. These two efficacy and safety studies, Studies COMB157RMS301 and COMB157RMS302, were both randomized, double-blind, double-dummy, active-controlled studies comparing ublituximab-xiiy to teriflunomide treatment in adult subjects with relapsing forms of MS. These trials were identical in design with the same primary efficacy outcome measure, ARR,

along with the same secondary endpoints that were analyzed in a hierarchical analysis.

Regulatory History

Dr. Laura Baldassari's clinical review provides the full regulatory history of the development program for ublituximab-xiiy for the treatment of relapsing forms of MS.

The applicant opened IND 127265 for ublituximab-xiiy as a proposed treatment of MS on October 16, 2015. There was a Type C meeting to discuss Phase 3 trial design with written responses issued on July 8, 2016. The applicant submitted an initial request for Special Protocol Assessments of the protocols for its identical Phase 3 studies on September 23, 2016, and, after reviewing several submissions with no agreement, the Division issued SPA agreements for both protocols on July 29, 2017.

During the conduct of the Phase 3 trials, the Division had concerns related to the safety of ublituximab-xiiy as well as safety reporting (see Section 11.) When several serious infections and three deaths were reported in the MS development program in 2019, the Division requested that the applicant update the informed consent documents and Investigator's Brochure, reconsent subjects, and inform investigators of the apparent increased risk of life-threatening and serious infections. These requests were communicated to the applicant on December 18, 2019.

There was a pre-BLA meeting held on April 6, 2021, and the applicant submitted BLA 761238 on September 28, 2021.

Of note, on January 13, 2022, the Division of Hematologic Malignancies II placed a partial clinical hold on (b) (4) as a potential treatment for chronic lymphocytic leukemia because of an imbalance in deaths favoring the ublituximab and umbralisib arm as compared with the active comparator treatment arm using standard of care treatments. The partial hold, which stipulated that no new subjects could be recruited to any ongoing trials, noted that "… the overall survival data, toxicity data, including treatment modifications due to an adverse event, and pharmacokinetic data, including positive exposure-response for safety for both ublituximab and umbralisib, suggest the adequacy of the selected dose or regimen of umbralisib and/or ublituximab is uncertain." After review of a complete response to hold submitted by the applicant, on April 14, 2022, the Division of Hematologic Malignancies II continued the partial clinical hold and suggested that the applicant consider a separate investigation of ublituximab as a potential monotherapy for chronic

lymphocytic leukemia. On April 15, 2022, the applicant announced a discontinuation of the development of umbralisib for all indications and withdrew both submitted licensing applications for the umbralisib-ublituximab combination therapy. The applicant's decision to discontinue development of the combination therapy for hematological malignancies was based on an unfavorable risk-benefit assessment of umbralisib, not ublituximab.

2. Product Quality

The Office of Biotechnology Products (OBP) provided an integrated review. Refer to the OBP review for the full listing of the OBP review team. The OBP team recommends approval.

General Product Quality Considerations

The OBP team's review of manufacturing identified that the methodologies used for drug substance and drug product manufacturing, release, and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The team concluded that the BLA is recommended for approval from sterility assurance and microbiology product quality perspectives as well.

Postmarketing Commitments

To address several product quality issues noted during review, four post-marketing commitments (PMC) were discussed and agreed to by the applicant during the BLA review. These PMCs are summarized in Section 13 of this memorandum.

Facilities Review/Inspection

All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent inspections.

3. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Barbara Wilcox. Dr. Lois Freed provided a supervisory review. Dr. Wilcox recommends approval, and Dr. Freed concurs. The principal conclusions of Dr. Wilcox's and Dr. Freed's reviews were as follows:

- In all the general toxicology studies, the observed findings were considered to be the result of the known pharmacodynamic activity of ublituximab-xiiy. These included near total depletion of B-lymphocyte populations within 24

hours after the first dose and the depletion of B-cell populations from lymphoid tissues.

- An enhanced pre- and postnatal development study was conducted using subsets of animals, dosed during the first, second, or third trimester, to ensure, to the extent possible, adequate exposure throughout gestation. However, ublituximab was substantially more immunogenic in pregnant animals, which resulted in maternal morbidity and death and embryofetal loss. Because of the deaths in dams dosed during the first and second trimesters, only 2 dams were dosed during the third trimester.

- External, viscera, and skeletal abnormalities occurred in two infants from dams exposed to ublituximab during the second trimester of pregnancy. Findings in infants included contractures and abnormal flexion of multiple limbs and tail, shortened mandible, elongate calvarium, enlargement of ears, and/or craniomandibular abnormalities which were attributed to histopathological brain necrosis. Histopathology evaluations revealed minimal to moderate degeneration/necrosis in the brain. Abnormalities were absent in infants of dams exposed during the first trimester of pregnancy. A no-effect dose for adverse effects on embryofetal development in monkeys was not identified and this failure to identify a no-effect dose is described in labeling.

- To support future clinical development of ublituximab in pediatric patients, the sponsor will need to address the potential for adverse effects on the developing immune system by conducting a juvenile animal toxicology study in animals of an appropriate age. If such a study were not feasible, the sponsor would need to provide justification with supportive data for that conclusion and any other data that may be available to address this safety concern. A postmarketing requirement was issued for this study (see Section 13).

4. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) Review was written by Drs. Anantha Ram Nookala, Vishnu Sharma, Atul Bhattaram, and Gopichand Gottipati. The signatory was Dr. Mehul Mehta. The OCP team recommends approval.

The OCP review's conclusions regarding key review topics were as follows:

1. Ublituximab-xiiy appears to be effective in reducing relapses due to MS in two Phase 3 randomized, multicenter, double-blind, double-dummy, active-controlled studies.

2. The dosing regimen that was used in the Phase 3 trials demonstrating substantial evidence of effectiveness was 150 mg administered by intravenous infusion over 4 hours on Day 1, followed by 450 mg by intravenous infusion over 1 hour on Day 15. Subsequent infusions were 450 mg intravenous infusions over 1 hour administered every 6 months. This regimen effectively depleted CD20+ B-cells in a consistent and sustained manner. A higher dose of ublituximab-xiiy (600 mg) did not appear to provide different pharmacodynamic effects that would suggest a potential for superior efficacy compared to the 450 mg maintenance dose.

3. No dose adjustments are needed for ublituximab-xiiy based on age, race, sex, weight, renal or hepatic impairment, food-intake, or metabolic/transporter mediated interactions.

4. The applicant conducted analytical comparability studies to establish a bridge between to-be-marketed product and the formulation used in the Phase 3 clinical studies (TG1101-RMS301 and TG1101-RMS302). The OBP team confirmed that the two products are analytically comparable, and therefore, the scientific bridge is acceptable.

5. The original neutralizing antibody assay used during the clinical trials was not sensitive enough to detect low level of positive control in the presence of high concentrations of ublituximab-xiiy. In a communication from the applicant dated September 30, 2022, the applicant agreed to develop a neutralization assay and submit a full validation report of the newly developed neutralization assay, re-analyze neutralizing antibody in patients enrolled in the Phase 3 clinical studies (TG1101-RMS301 and TG1101-RMS302), and to evaluate the potential impact on the pharmacokinetics, pharmacodynamics, safety, and efficacy of ublituximab-xiiy. See Section 13 of this memorandum for a description of this postmarketing commitment. Based on the data submitted using the original assay, there were no obvious immunogenicity effects on efficacy or safety in the Phase 3 clinical trials but results from a more sensitive assay are needed to provide reassurance of the appropriateness of this conclusion.

6. Clinical Microbiology

See Section 3, Product Quality.

7. Clinical/Statistical- Efficacy

Dr. Laura Baldassari was the clinical efficacy reviewer for this application; Dr. Paul R. Lee was the clinical Team Leader. Dr. Xiang Ling was the biometrics reviewer, and Dr. John Lawrence was the biometrics Team Leader. Dr. Baldassari finds that the application provides substantial evidence of effectiveness for ublituximab-xiiy in the treatment of subjects with relapsing forms of MS. Drs. Ling and Lawrence agree that the application provides adequate statistically significant findings for the trial's primary efficacy outcome measure; the biometrics team recommends approval.

Study Design

The applicant submitted data from two adequate and well-controlled efficacy studies, Study TG1101-RMS301 (hereafter "Study RMS301"), and Study TG1101-RMS302 (hereafter "Study RMS302"). These studies were identical Phase 3, multinational, randomized, double-blind, double-dummy, parallel-group, active-controlled studies that evaluated intravenous ublituximab-xiiy compared to oral teriflunomide. Both studies were conducted using protocols with agreed Special Protocol Assessments.

The treatment durations for subjects in both of these studies were a 96-week blinded observation period followed by a follow-up period of 20 weeks of open-label treatment with ublituximab-xiiy. Subjects enrolled in these trials were not permitted to receive other chronic immune treatments for MS, and there were exclusion criteria and allowances for adequate treatment abstinence periods prior to randomization designed to prevent carry over of previous treatments' effects into the controlled trial phase. Subjects could continue dalfampridine at a stable dose during the trial and corticosteroids could be administered for acute treatment of relapses and as premedication to prevent infusion-related reactions. The inclusion criteria for Studies RMS301 and RMS302 were a diagnosis of a relapsing form of MS using the standard international 2010 Revised McDonald criteria, and documentation of at least 1 relapse during the previous 1 year, or 2 relapses during the previous 2 years prior to screening, or a positive gadolinium-enhancing T1 lesion on magnetic resonance imaging (MRI) scan during the year prior to randomization.

Relapses were assessed by an Independent Relapse Adjudication Panel (IRAP). Only relapses assessed by the IRAP as being per-protocol relapses were included in the primary efficacy analysis, and the IRAP remained blinded to study treatment as did

all study staff. Neuroimaging studies were examined by a central reading center which did not receive treatment assignment nor clinical information regarding subjects.

Subjects who experienced new or worsening neurologic symptoms were instructed to contact the treating neurologist within 48 hours of symptom onset. Within 7 days of the subject reporting the suspected relapse to the treating neurologist, the subject was scheduled for a study visit and assessed by both the treating and examining neurologist independently. Relapse assessments included neurological and physical examinations, review of concomitant medications, safety assessment, and Expanded Disability Status Scale (EDSS, by the examining neurologist). The treating neurologist was blinded to the examining neurologist's EDSS assessment. After the completion of the examining neurologist's assessment, the treating neurologist was permitted to initiate relapse treatment with intravenous methylprednisolone 1 gram daily for 3 to 5 days.

The results of the treating and examining neurologists' assessments were then sent to IRAP for confirmation. Relapses were confirmed if a subject experienced either a 2-point or greater increase on one, or a 1-point increase on 2 or more of the appropriate Functional Systems (which correspond to the subject's symptoms), or at least a 0.5-point increase in EDSS (unless EDSS was 0, which required an increase of at least 1 point) from the previous assessment. Additionally, relapses were defined in the protocol as "new or worsening neurological symptoms lasting at least 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." Relapses were also to be preceded by neurological stability for at least 30 days.

The primary efficacy endpoint for Studies RMS301 and RMS302 was the ARR defined as the number of IRAP-confirmed relapses per subject year. The estimate of ARR for a treatment group was the total number of relapses for subjects in the respective treatment group divided by the sum of treatment duration for subjects in that specific treatment group, and all subjects were exposed to blinded treatment for 96 weeks.

The hierarchically ordered secondary efficacy endpoints (analyzed in the following order) were:

- Total number of gadolinium-enhancing T1-lesions per MRI scan by Week 96.
- Total number of new and enlarging T2 hyperintense lesions per MRI scan by Week 96.

- Time to Confirmed Disability Progression (CDP) for at least 12 weeks occurring during the 96-week double-blind treatment period. This analysis utilized pooled data from RMS301 and RMS302.
- Proportion of subjects with No Evidence of Disease Activity (NEDA) from Week 24 to Week 96.
- Proportion of subjects reaching impaired Symbol Digit Modalities Test (SDMT) from Baseline to Week 96.
- Percentage change in brain volume from Baseline to Week 96.

Study RMS301

Demographics

In Study RMS301, the intention-to-treat (ITT) population, defined as every subject randomized to treatment, was comprised of a total of five hundred forty-five (545) subjects, with 271 (49.7%) randomized to treatment with ublituximab-xiiy and 274 (50.3%) randomized to treatment with teriflunomide. Most (89.5%) of the enrolled subjects came from Eastern Europe, and 8.8% came from the United States.

The ITT population in Study RMS301 was 63.3% female, had a median and mean age of 36.6 and 36.0 years old, respectively, and 97.3% of the subjects were White. These demographic data are consistent with the well-established demographics of the worldwide population diagnosed with a relapsing form of MS. The ITT population was adequately balanced between treatment arms with respect to these and other key demographic and baseline disease variables.

Overall, 492 (90.3%) of all subjects completed the 96-week blinded treatment period; 240 (87.6%) of the ublituximab-xiiy-treated subjects and 252 (91.6%) of the teriflunomide-treated subjects, respectively completed Study RMS301 on treatment. The two most common reasons for permanent treatment discontinuation across both treatment arms were subject withdrawal of consent (3.8%) and adverse events (3.3%). There was an imbalance between treatment arms with respect to withdrawal rates due to adverse events (6.2% ublituximab-xiiy vs. 0.4% teriflunomide). There was also an imbalance between treatment arms with respect to subject withdrawal of consent (2.2% ublituximab-xiiy vs. 5.5% teriflunomide). There was no indication of systematic unblinding as a possible explanation for the discrepancies in discontinuations between treatment arms.

Primary Outcome Measure

The primary efficacy endpoint was the ARR, which the applicant calculated as a group ARR utilizing treatment duration in years and number of IRAP-confirmed

clinical relapses. In Study RMS301, there were 36 (13.3%) subjects treated with ublituximab-xiiy who experienced a total of 44 IRAP-confirmed relapses; there were 68 (24.8%) subjects treated with teriflunomide who had a total of 111 IRAP-confirmed relapses. There were similar rates of relapse confirmation by the IRAP in both treatment arms in Study RMS301 (66.7% [44/66 relapses] confirmed in the ublituximab group and 73.0% [111/152] confirmed in the teriflunomide group.)

The primary efficacy analysis of the ARR was a negative binomial regression model that included the total number of confirmed relapses with onset between randomization date and the day of last treatment as response variable, treatment group, EDSS strata (baseline EDSS score less than or equal to 3.5 versus greater than 3.5), and clinical site region (USA and Western Europe, Eastern Europe) as covariates. To account for any different treatment durations among subjects, the log-transformed standardized treatment duration was included in the model as an "offset" variable. For participants who withdrew from their active treatment, all data up to the time of withdrawal from treatment were used in the primary analysis.

The following table, adapted from the biometrics review, provides the results of the primary efficacy analysis:

Table 1: Study RMS301: Summary of Annualized Relapse Rate (ARR)

	Ublituximab-xiiy N=271	Teriflunomide N=274
Least Squares Mean ARR (95% confidence interval)	0.076 (0.042, 0.138)	0.188 (0.124, 0.283)
Rate ratio (95% confidence interval)	0.406 (0.268, 0.615)	
Percentage reduction	59.4%	
p-value	<0.0001	

Source: Biometrics Review, Table 3

The primary efficacy analysis of Study RMS301 was highly statistically significant ($p<0.0001$) in favor of ublituximab-xiiy in subjects with relapsing forms of MS. Drs. Baldassari and Ling agree that the ARR outcome of the primary efficacy analysis is convincing evidence of a significant treatment effect of ublituximab-xiiy that exceeds the established efficacy of teriflunomide in the prevention of relapses in MS.

Dr. Ling confirmed the ARR results remained highly significant in all of the applicant's pre-planned sensitivity analyses as follows:

1. The primary analysis was repeated using all reported MS relapses (rather than just IRAP-confirmed relapses).

2. An analysis of time to first IRAP-confirmed relapse using a Cox proportional hazards model that included treatment, region, number of relapses in previous year, baseline EDSS score strata, baseline number of T1 gadolinium-enhancing lesions, sex, and the subject's age at Baseline as covariates.

3. To assess the effects of treatment withdrawals, the primary analysis was repeated including relapses which occurred after permanent discontinuation of study medication and natural log (time on study in years) was used as the offset variable.

4. To assess the impact of the discontinuation from the trial for all participants who provided withdrawal of consent, excluding deaths, multiple imputation was used to impute the expected number of relapses a participant would have had if they had continued to participate in the trial. To perform the imputation, ten replicates were used since a relapse on treatment was a relatively low frequency event. The covariates used to model and predict the imputations included treatment, region, number of relapses in previous year, baseline EDSS score strata, baseline number of T1 gadolinium-enhancing lesions, sex and age.

The biometrics reviewer also confirmed the applicant's results from exploratory subgroup analyses for age, gender, race, and geographical region, with a comment that several subgroups (race other than White and United States participants) were numerically small and therefore generated results that, while trending similarly to the overall group results, were difficult to interpret because of the small sample sizes. These two subgroups (non-White and United States subjects) are generally small in multinational trials; MS disproportionately affects White subjects and the medical standard of care for MS in the United States makes trial enrollment less appealing than in countries which lack access to highly effective MS treatments. The findings from these small subgroups do not undermine a conclusion that the exploratory subgroup analyses suggest that the ublituximab-xiiy treatment on ARR appears to be consistently robust and preserved in all of these subgroups.

Secondary Outcome Measures

Gadolinium-enhancing T1 Lesions and New or Enlarging T2 Hyperintense Lesions

The following tables, adapted from the biometrics review, provide the confirmed results of the secondary outcome efficacy analyses of MRI outcomes (gadolinium-enhancing T1 lesions and new or enlarging T2 lesions) which were analyzed as negative binomial regressions with the same statistical considerations as in the primary outcome analysis:

Table 2: Study RMS301: Summary of Gadolinium-enhancing T1 Lesions per MRI scan per Subject

	Ublituximab-xiiy N=265	Teriflunomide N=270
Least Squares Mean Number of T1 Gadolinium-enhancing Lesions (95% confidence interval)	0.016 (0.008, 0.032)	0.491 (0.355, 0.679)
Rate ratio (95% confidence interval)	0.033 (0.019, 0.058)	
Percentage rate reduction	96.7%	
p-value	<0.0001	

Source: Biometrics Review, Table 4

Table 3: Study RMS301: Summary of New or Enlarging T2 Hyperintense Lesions per MRI scan per Subject

	Ublituximab-xiiy N=260	Teriflunomide N=267
Least Square Mean Number of New/enlarging T2 lesions (95% confidence interval)	0.213 (0.144, 0.316)	2.789 (2.136, 3.643)
Rate ratio (95% confidence interval)	0.076 (0.056, 0.104)	
Percentage rate reduction	92.4%	
p-value	<0.0001	

Source: Biometrics Review, Table 4

The MRI outcome findings show a robust, statistically significant treatment effect of ublituximab-xiiy in reducing the number of gadolinium-enhancing T1 and new or enlarging T2 hyperintense lesions on MRI scans. These MRI outcomes provide

additional support for a treatment effect of ublituximab-xiiy on MS and are consistent with the highly significant primary outcome analysis finding of a reduction in ARR.

Time to Confirmed Disability Progression (CDP) for at least 12 weeks

The disability-related key secondary outcome assessment of disability progression confirmed for at least 12 weeks (3 months) is based on an analyses of the pooled data from Studies RMS301 and RMS302 because each individual trial would not be adequately powered to provide individual study outcome analyses of these relatively small number of outcomes.

The following table and figure, taken from the biometrics review, summarizes the time to 12 weeks (minimum) confirmed disability worsening in both trials:

Table 4: Studies RMS301 and RMS302: Time to Confirmed Disability Progression for at Least 12 Weeks

	Ublituximab-xiiy N=543	Teriflunomide N=546
Number of Subjects with Confirmed Disability Progression for at least 12 weeks	28 (5.2%)	32 (5.9%)
Hazard ratio (95% confidence interval)	0.843 (0.504, 1.407)	
p-value	0.5099	

Source: Biometrics review, Table 5

The analysis of the time to 12-week (at least) disability progression was not statistically significant (p=0.5099). The total number of subjects with confirmed disability progression was small (60 subjects, 11% of the total study population). The existence of so few subjects with confirmed disability progression in these two trials is to be expected because progression of disability is a rare event in trials, the other anti-CD20 therapies approved to treat MS demonstrated a significant treatment effect on disability progression, and because teriflunomide itself has a significant established treatment effect on disability progression. The statistical analysis of this endpoint was intended to show superiority of ublituximab-xiiy over teriflunomide which is a very difficult outcome to achieve given teriflunomide's established efficacy and such a small pool of events. It is possible that ublituximab-xiiy has a treatment effect on disability that is equivalent to teriflunomide's, but such a determination would have required a different statistical design and cannot be inferred from this non-significant superiority outcome analysis result.

The applicant provided an exploratory analysis of time to 24-week confirmed disability which was also not significant (hazard ratio 0.657, nominal p=0.1716) which provides further evidence of a lack of relatively greater treatment effect for ublituximab-xiiy in comparison to teriflunomide, an active comparator which has demonstrated efficacy on disability progression in MS.

Other Secondary Outcome Measures

Given that the analysis of confirmed disability progression was not statistically significant, subsequent analyses of the remainder of the key secondary endpoints (Proportion of subjects with No Evidence of Disease Activity (NEDA) from Week 24 to Week 96, proportion of subjects reaching impaired Symbol Digit Modalities Test (SDMT) from Baseline to Week 96, and Percentage change in brain volume from Baseline to Week 96) in the hierarchical analysis were not tested.

Study RMS302

Study Design

The design of Study RMS302 was identical to that of Study RMS301. This study also was conducted with a protocol that had an agreed-upon Special Protocol Assessment.

Demographics

In Study RMS302, the intention-to-treat (ITT) population, defined as every subject randomized to treatment, was comprised of a total of five hundred forty-four (544) subjects, with 272 (50.0%) randomized to treatment with ublituximab-xiiy and 272

(50.0%) randomized to treatment with teriflunomide. Most (91.0%) of the enrolled subjects came from Eastern Europe, and 6.6% came from the United States.

The ITT population in Study RMS302 was 65.1% female, had a median and mean age of 35.3 and 35.0 years old, respectively, and 98.7% of the subjects were White. These demographic data are entirely consistent with the well-established demographics of the worldwide population diagnosed with a relapsing form of MS. The ITT population was adequately balanced between treatment arms with respect to these and other key demographic and baseline disease variables.

Overall, 493 (90.5%) of all subjects completed the 96-week blinded treatment period; 254 (93.4%) of the ublituximab-xiiy-treated subjects and 239 (87.5%) of the teriflunomide-treated subjects, respectively completed Study RMS302 on treatment. The most common reasons for permanent treatment discontinuation across both treatment arms were subject withdrawal of consent (5.3%), pregnancy (0.9%), adverse events (0.7%), and investigator decision (0.7%). As in Study RMS 301, there was an imbalance between treatment arms with respect to withdrawal rates due to adverse events (1.1% ublituximab-xiiy vs. 0.4% teriflunomide). Pregnancy accounted for a higher percentage of withdrawals in the ublituximab-xiiy treatment arm (1.5% versus 0.4%) which has no obvious explanation beyond a random chance imbalance. As was also the case in Study RMS301, there was imbalance between treatment arms with respect to subject withdrawal of consent (2.2% ublituximab-xiiy vs. 8.4% teriflunomide). There was no indication of systematic unblinding as a possible explanation for the discrepancies between treatment arms.

Primary Outcome Measure

The primary efficacy endpoint was the ARR, which the applicant calculated as a group ARR utilizing treatment duration in years and number of IRAP-confirmed clinical relapses. In Study RMS302, there were 34 (12.5%) subjects treated with ublituximab-xiiy who experienced a total of 53 IRAP-confirmed relapses; there were 72 (26.5%) subjects treated with teriflunomide who had a total of 102 IRAP-confirmed relapses. There was a numerical difference between the rates of relapse confirmation by the IRAP between the treatment arms in Study RMS302, 70.7% or 53/75 relapses) confirmed in the ublituximab-xiiy group as compared to 88.7% (102/115) confirmed in the teriflunomide group. A review of IRAP patient files requested by Dr. Baldassari revealed no systematic bias nor evidence of the sharing of unblinded information to explain the higher rate of confirmation in subjects treated with ublituximab-xiiy. As indicated below, a sensitivity analysis including all relapses was also statistically significant (p=0.0193) which confirms that the observed treatment effects on relapses were consistent regardless of IRAP confirmation.

The primary efficacy analysis of the ARR was a negative binomial regression model that included the total number of confirmed relapses with onset between randomization date and the day of last treatment as response variable, treatment group, EDSS strata (baseline EDSS score less than or equal to 3.5 versus greater than 3.5), and clinical site region (USA and Western Europe, Eastern Europe) as covariates. To account for any different treatment durations among subjects, the log-transformed standardized treatment duration was included in the model as an "offset" variable. For participants who withdrew from their active treatment, all data up to the time of withdrawal from treatment were used in the primary analysis.

The following table, adapted from the biometrics review, provides the results of the primary efficacy analysis:

Table 5: Study RMS302: Summary of Annualized Relapse Rate (ARR)

	Ublituximab-xiiy N=272	Teriflunomide N=272
Least Squares Mean ARR (95% confidence interval)	0.091 (0.049, 0.169)	0.178 (0.109, 0.291)
Rate ratio (95% confidence interval)	0.509 (0.330, 0.784)	
Percentage reduction	49.1%	
p-value	0.0022	

Source: Biometrics Review, Table 8

The primary efficacy analysis of Study RMS301 was highly statistically significant (p=0.0022) in favor of ublituximab-xiiy in subjects with relapsing forms of MS. Drs. Baldassari and Ling agree that the ARR outcome of the primary efficacy analysis is convincing evidence of a significant treatment effect of ublituximab-xiiy that exceeds the established efficacy of teriflunomide in the prevention of relapses in MS. The findings in Study RMS302 for ARR are very similar to, and replicate, the statistically significant findings of Study RMS301.

Dr. Ling confirmed the ARR results remained highly significant in all of the applicant's pre-planned sensitivity analyses (which were identical the analyses in RMS301) as follows:

1. The primary analysis was repeated using all reported MS relapses (rather than just IRAP-confirmed relapses).

2. An analysis of time to first IRAP-confirmed relapse using a Cox proportional hazards model that included treatment, region, number of relapses in previous year, baseline EDSS score strata, baseline number of T1 gadolinium-enhancing lesions, sex, and the subject's age at Baseline as covariates.

3. To assess the effects of treatment withdrawals, the primary analysis was repeated including relapses which occurred after permanent discontinuation of study medication and natural log (time on study in years) was used as the offset variable.

4. To assess the impact of the discontinuation from the trial for all participants who provided withdrawal of consent, excluding deaths, multiple imputation was used to impute the expected number of relapses a participant would have had if they had continued to participate in the trial. To perform the imputation, ten replicates were used since a relapse on treatment was a relatively low frequency event. The covariates used to model and predict the imputations included treatment, region, number of relapses in previous year, baseline EDSS score strata, baseline number of T1 gadolinium-enhancing lesions, sex and age.

The biometrics reviewer also confirmed the applicant's results from exploratory subgroup analyses for age, gender, race, and geographical region. As was noted in the review of Study RMS301, the biometrics reviewer commented that several subgroups (race other than White and United States participants) were numerically small and therefore generated results that, while trending similarly to the overall group results, were difficult to interpret because of the small sample sizes. These two subgroups (non-White and United States subjects) are generally small in multinational trials; MS disproportionately affects White subjects and the medical standard of care for MS in the United States makes trial enrollment less appealing than in countries which lack access to highly effective MS treatments. The findings from these small subgroups do not undermine a conclusion that the exploratory subgroup analyses suggest that the ublituximab-xiiy treatment on ARR appears to be consistently robust and preserved in all of these subgroups.

Secondary Outcome Measures

Gadolinium-enhancing T1 Lesions and New or Enlarging T2 Hyperintense Lesions

The following tables, adapted from the biometrics review, provide the confirmed results of the secondary outcome efficacy analyses of MRI outcomes (gadolinium-

enhancing T1 lesions and new or enlarging T2 lesions) which were analyzed as negative binomial regressions with the same statistical considerations as in the primary outcome analysis:

Table 6: Study RMS302: Summary of Gadolinium-enhancing T1 Lesions per MRI scan per Subject

	Ublituximab-xiiy N=272	Teriflunomide N=267
Least Squares Mean Number of T1 Gadolinium-enhancing Lesions (95% confidence interval)	0.009 (0.004, 0.017)	0.250 (0.162, 0.385)
Rate ratio (95% confidence interval)	0.035 (0.019, 0.064)	
Percentage rate reduction	96.5%	
p-value	<0.0001	

Source: Biometrics Review, Table 9

Table 7: Study RMS302: Summary of New or Enlarging T2 Hyperintense Lesions per MRI scan per Subject

	Ublituximab-xiiy N=272	Teriflunomide N=267
Least Square Mean Number of New/enlarging T2 lesions (95% confidence interval)	0.282 (0.200, 0.397)	2.831 (2.128, 3.767)
Rate ratio (95% confidence interval)	0.100 (0.073, 0.136)	
Percentage rate reduction	90.0%	
p-value	<0.0001	

Source: Biometrics Review, Table 9

The MRI outcome findings show a robust statistically significant treatment effect of ublituximab-xiiy in reducing the number of gadolinium-enhancing T1 and new or enlarging T2 hyperintense lesions on MRI scans. These MRI outcomes provide additional support for a treatment effect of ublituximab-xiiy on MS and are consistent with the highly significant primary outcome analysis finding of a reduction in ARR. These findings are also very consistent with the MRI outcomes in Study RMS301.

Other Secondary Endpoints

As indicated in the discussion of the results of Study RMS301, the combined analysis of confirmed disability data from both studies was not statistically significant. Therefore, all subsequent secondary endpoints were not tested.

Conclusions on the Substantial Evidence of Effectiveness

Approval for Briumvi (ublituximab-xiiy) for relapsing forms of MS is supported by efficacy findings from two adequate and well-controlled clinical trials, Studies RMS301 and RMS302. These studies demonstrated that ublituximab-xiiy treatment yielded consistent statistically significant reductions of 59.4% and 49.1% in ARR, respectively, relative to an active comparator, teriflunomide. A reduction of over 50% in ARR averaged across the two studies is a robust and meaningful outcome for a therapy intended to treat relapsing forms of MS. In these studies, a significant treatment effect on ARR was established relative to teriflunomide, an active comparator with its own significant treatment effect on ARR, and therefore one would predict an even more robust and clinically meaningful reduction in relapses for ublituximab in comparison to no treatment. The significant MRI findings in these two studies provide additional supportive findings that suggest a strong treatment effect on MS-related pathology.

The failure to demonstrate a treatment effect on disability progression is a notable difference from findings with other approved anti-CD20 therapies but may be attributable to the statistical difficulty in establishing superiority over an active comparator which has itself demonstrated a significant reduction in disability. One may speculate that ublituximab-xiiy's treatment effect on disability overlaps with that of teriflunomide, and the small number of disability progression events rendered it statistically impossible to demonstrate superiority of ublituximab-xiiy over the active comparator.

Nevertheless, based on the robustly significant findings for the primary relapse endpoint in two identical trials, these studies have provided substantial evidence of effectiveness for ublituximab-xiiy in the treatment of subjects with relapsing forms of MS by showing a strong treatment effect on relapses.

8. Safety

Dr. Laura Baldassari was the clinical safety reviewer for this application.

According to Dr. Baldassari's review, 916 unique subjects with MS were exposed to at least one dose of ublituximab-xiiy in the MS development program. Of these 916

subjects, 868 subjects were exposed to at least one dose of the intravenous regimen proposed for the treatment of relapsing forms of MS. The comparator in Studies RMS301 and RMS302 was teriflunomide, an approved therapy for relapsing forms of MS with a well-characterized safety profile. While there have been trials investigating ublituximab-xiiy as a treatment for leukemia, Dr. Baldassari's safety review focused on findings only from trials in subjects with relapsing forms of MS because the studies in leukemia used to support a now withdrawn BLA for ublituximab-xiiy as a potential leukemia therapy were conducted in a setting of a chronic fatal cancer with concurrent use of multiple potent immune suppressing agents. Therefore, the applicability of these findings to the MS population were deemed to be very limited and would not be informative, especially given that the size of the MS development program safety database which provides relevant, interpretable, and generalizable findings for the MS population.

The following table, adapted from a table in Dr. Baldassari's review, summarizes the extent of exposure to ublituximab-xiiy in the applicant's development program for relapsing forms of MS:

Table 8: Ublituximab-xiiy Safety Population Duration of Exposure

Duration of Exposure	Briumvi (N=916)
≥ 6 months	565
≥ 12 months	547
≥ 18 months	358
≥ 24 months	354
All Exposed ≥ 1 dose	916

Source: Clinical Safety Review, Table 47

The safety database consisting of 916 exposed subjects with MS, with 547 subjects with MS exposed for at least 1 year, is adequate with respect to number exposed and duration of exposure for generating meaningful safety conclusions regarding the MS indication. Approximately two-thirds (63.3%) of the subjects exposed for more than one year were women, 68.4% were less than 40 years old, and 98.2% were White, all of which are consistent with the demographics of the worldwide population with relapsing forms of MS.

Deaths

There were three deaths (3/545, 0.6%) reported in ublituximab-xiiy-exposed subjects in the blinded treatment phases of Studies RMS301 and RMS302.

Study RMS301

There were two deaths (2/271, 0.7%) in this study.

1. Subject (b) (6) was a 32-year-old woman with relapsing-remitting MS and no other relevant medical history who was hospitalized from (b) (6) after contracting measles on (b) (6) (Study Day 365). The subject had childhood vaccinations for measles and no booster vaccinations in adulthood. She had received four doses of investigational therapy (ublituximab-xiiy) at this time, with the most recent dose administered on (b) (6) Her symptoms initially included generalized weakness and rhinorrhea, then, on the day of hospitalization, she developed rash, fever, headache, cough, bronchitis, and conjunctivitis leading to hospitalization. After discharge, she then experienced an investigator-confirmed relapse on (b) (6) which was characterized by left sided weakness and ataxia, gait ataxia, and abnormal left-sided involuntary movements beginning on the day prior to presentation. She was treated for this relapse from (b) (6) with methylprednisolone. On (b) (6) she experienced tonic-clonic seizures with loss of consciousness and was hospitalized. A lumbar puncture obtained on admission revealed no remarkable findings, but an electroencephalogram (EEG) was notable for "irritations [sic] effects, signs of convulsive readiness of the brain and high threshold of excitability." Seizures continued, and her condition gradually deteriorated despite treatment for bacterial and viral meningoencephalitis. A repeat lumbar puncture on (b) (6) noted "neutrophilic pleocytosis" but other testing was unrevealing. She became comatose on (b) (6) and repeat lumbar puncture obtained at this time revealed a negative measles virus assay in cerebrospinal fluid with a positive serum rubella IgG. The patient required mechanical ventilation beginning (b) (6) She died on (b) (6) Autopsy findings (meningoencephalitis consistent with rubella measles and bilateral interstitial giant cell pneumonia) were consistent with disseminated measles as the cause of death. The applicant deemed this death to be unrelated to study treatment, but a disseminated infection in the setting of immune suppression is not only plausible with ublituximab-xiiy treatment, but exposure to this therapy is the only identifiable risk factor for a vaccinated, previously healthy adult subject experiencing fatal complications due to measles.

2. Subject (b) (6) was a 22-year-old woman with relapsing-remitting MS and no other relevant medical history who was found to have an ectopic pregnancy on (b) (6) (Study Day 550). She had received five doses of

investigational treatment (ublituximab-xiiy) at this time, with the most recent administration on (b) (6). She underwent a left-sided tubotomy and salpingostomatoplasty, and she was discharged from the hospital with the event reported resolved on (b) (6). The subject did not present for routine surgical follow-up and reportedly experienced left lower abdominal pain, nausea, vomiting, fever, and constipation in early (b) (6). Her condition deteriorated leading to hospitalization on (b) (6). On admission, examination revealed salpingitis and an infected post-surgical wound, with infiltration of the abdominal cavity, partial intestinal obstruction, and findings consistent with sepsis. Despite broad spectrum antibiotic treatment, and four attempts at surgical drainage, the subject died on (b) (6). An autopsy revealed the cause of death was "sepsis, toxicosis, perforation of the sigmoid colon and small intestine, peritonitis, pelvioperitonitis, abdominal abscesses and left-sided purulent salpingitis." The applicant assessed this death as unrelated to study treatment, but immune suppression from almost two years of ublituximab-xiiy exposure is a plausible etiology, and the most likely explanation, for a young and otherwise healthy subject with MS dying of sepsis almost four months after a surgical procedure.

Study RMS302

There was one death (1/272, 0.4%) in this study.

1. Subject (b) (6) was a 36-year-old man with relapsing-remitting MS and a history of chronic sinusitis who was diagnosed with pneumonia on (b) (6) (Study Day 476). He had received four doses of investigational treatment (ublituximab-xiiy) with the most recent administration on (b) (6). He had experienced shortness of breath, decreased exercise tolerance, and fever for more than 7 days prior to hospitalization on (b) (6) and he was being treated with azithromycin for presumed community-acquired pneumonia. He presented to the hospital with dyspnea, cyanosis, and diffuse edema. He was assessed as hypotensive with evidence of heart failure, and his condition deteriorated rapidly. The subject died on the day of hospital admission. An autopsy listed the direct cause of death as pulmonary and cardiac insufficiency as a complication of bilateral purulent pneumonia with confluent foci. The applicant determined that the subject's death was possibly related to ublituximab-xiiy which is an appropriate conclusion given that a death from community acquired pneumonia is an unusual outcome in an otherwise healthy subject with MS treated with antibiotics and would be a rare but potential consequence of over a year of immune suppression induced by ublituximab-xiiy.

As noted in the regulatory history, the fact there were three deaths due to infection prompted the Division to request a notification to all investigators of these events and re-consenting of subjects in Studies RMS301 and RMS302. There were no further deaths in blinded treatment in either trial after the applicant acted on the Division's requests.

Serious Adverse Events

In Study RMS301, serious adverse events (SAEs) occurred in 31/271 subjects (11.4%) treated with ublituximab-xiiy and in 19/274 subjects (6.9%) treated with teriflunomide. The most frequently reported SAEs that were more common in ublituximab-xiiy treatment, categorically, were infections and infestations (5.5% vs. 2.2% in the teriflunomide comparator arm), and injury, poisoning, and procedural complications (1.5% vs. 0%). The most often reported infections were pneumonia (which occurred in three subjects treated with ublituximab-xiiy and no subjects treated with teriflunomide) and COVID-19 pneumonia (which occurred in two subjects treated with ublituximab-xiiy and in one teriflunomide-treated subject). Increased risk of infections, including serious infections, is a known consequence of the immune suppression achieved with anti-CD20 treatments. Labeling for risks of infection, including fatal infection, and a warning against the use of Briumvi in subjects with active infections should be adequate to mitigate this serious issue. The increased rate of procedural complications was attributable to a higher rate of injection-related reactions in the ublituximab-xiiy treatment group, which is expected in comparison to a comparator arm which featured an inert injection. The numerical discrepancy between treatment arms with respect to injury, poisoning, and procedural complications included three subjects with serious injuries (concussion, femoral neck fracture, and patellar fracture.) When reviewed, these injuries appeared unrelated to treatment with ublituximab-xiiy. The fourth subject experienced a serious infusion-related reaction; infusion-related reactions were among the most common complications of ublituximab-xiiy treatment and are also very common generally with anti-CD20 therapies given via infusion. Labeling will describe the pre-infusion mitigation strategy to reduce the severity of infusion-related reactions and will provide instructions for post-infusion monitoring. Ublituximab-xiiy will be administered in infusion centers with appropriate resources to manage the most serious infusion-related reactions which were noted to occur acutely during intravenous infusion.

In Study RMS302, SAEs occurred in 28/272 subjects (10.3%) treated with ublituximab-xiiy and in 21/272 subjects (7.7%) treated with teriflunomide. As in Study RMS301, the most common categorial SAEs were infections and infestations and pneumonia was

the most common infection (noted in 2 subjects treated with ublituximab-xiiy). Pneumonia was balanced between treatment arms with 2 subjects also experiencing pneumonia during teriflunomide treatment. Acute sinusitis and COVID-19 pneumonia were more common in ublituximab-xiiy treatment. This discrepancy in serious infections is not unexpected with a potent immune suppressant therapy, even with an active comparator, and labeling for risks of infection and warning against the use of Briumvi in subjects with active infections should be adequate to mitigate this serious issue. There was a numerical imbalance in subjects with cancer. Four subjects experienced a new diagnosis of a cancerous lesion during Study RMS302. Three of the four diagnosed cancers were gynecological (endometrial stromal sarcoma, uterine, and uterine leiomyoma.) Trials in subjects with MS tend to be yield safety databases with high rates of uterine and breast cancers because of the overlap in the demographics of MS and of gynecological cancers. Well over half of the study population in this study were women and, furthermore, these women were within the age range when these neoplastic diseases would initially present. It is therefore difficult to attribute these cancers to ublituximab-xiiy exposure since these cancer types are expected to occur in this trial population. There was not a clear overrepresentation of one form of cancer to suggest a more focused signal, none of these cancers appeared to have features to suggest abnormal presentation, and none were fatal. The periods of exposure to ublituximab-xiiy in the subjects diagnosed with cancer was variable and did not suggest a risk that emerged with longer exposures. It is also the case that systematic evaluation of this signal in postmarketing studies is very challenging because the ability to find an appropriate comparator group (subjects with MS treated with a competing similar therapy or a high-quality natural history database of MS patients) is logistically difficult, and any comparator group that is chosen will have a background rate of gynecological cancers for the reasons already described. Therefore, in the absence of a clear safety outcome to justify more elaborate monitoring, reliance on enhanced postmarketing reporting is acceptable as a means of further observation for this potential signal.

There was a numerical imbalance in COVID-19 pneumonia infections noted between the treatment groups. Given the challenging situation of conducting trials using immune suppressants during a global pandemic, attribution of a higher risk of serious COVID-19 infections with ublituximab-xiiy is difficult to support, especially since the COVID-19 outcomes captured during these trials do not reflect the current reality of the deployment of effective anti-viral treatments and vaccinations. There was a discrepancy between pneumonia due to other causes between the treatment conditions, too, and so higher rates of COVID-19 pneumonia in ublituximab-xiiy treatment would seem to align with a higher overall risk of any serious infection

attributable to ublituximab-xiiy, a risk which will be described as a Warning and Precautions in the approved Briumvi labeling.

In conclusion, ublituximab-xiiy treatment is associated with a risk of serious infections. Otherwise, aside from the specific risks discussed in this review, most SAEs in both of trials were isolated events. The safety database did not identify other broad categories of serious risks nor any new signals previously unseen in association with ublituximab-xiiy that had not been identified in the pre- and post-marketing safety databases of other approved intravenous anti-CD20 monoclonal antibody therapies.

Interruptions and Discontinuations

In Study RMS301, 6.6% of subjects receiving ublituximab-xiiy permanently discontinued study treatment as compared to 0.7% of subjects treated with teriflunomide. The most common reason for permanent discontinuation in this study, in two subjects (0.7%), was enteroviral meningitis. This form of meningitis is among the most common forms of viral meningitis, is typically not serious, and the subjects in this trial with enteroviral meningitis fully recovered after discontinuation of study treatment. This finding is not unexpected and will be subsumed within the already noted increased risk of infection that Briumvi labeling will describe. Other discontinuations were isolated events which are difficult to interpret given their singular nature, and none of these observed events demonstrated a potential pattern that requires further investigation.

In Study RMS302, the rate of permanent discontinuation of subjects in the ublituximab-xiiy treatment arm was lower than in Study RMS301 (1.8% as compared to 6.6%) while the teriflunomide treatment discontinuation rate remained 0.7%. There is no obvious explanation for the discrepancy between studies since they were identical in design and reporting rates should have been similar. All discontinuation events in this study were isolated and did not suggest a pattern. A case of hepatitis B was observed in an ublituximab-xiiy exposed subject who discontinued treatment. All other approved anti-CD20 therapies are associated with hepatitis B reactivation. Briumvi labeling will describe potential for hepatitis B reactivation since this is considered a class treatment effect because it has been observed with all other approved anti-CD20 monoclonal antibody therapies.

Treatment-Emergent Adverse Events

The following table, adapted from Dr. Baldassari's safety review, summarizes the most common treatment-emergent adverse events (TEAEs) that occurred in clinical trial subjects in the blinded portions of Studies RMS301 and RMS302:

Table 9: Treatment Emergent Adverse Events by Preferred Term, TEAEs Occurring in ≥5% of Ublituximab-Treated Subjects, Pooled Analysis of Phase 3 Double-Blind Data

	Ublituximab (N = 543)	Teriflunomide (N = 546)
Total Subjects with any Adverse Events	486 (89.5%)	501 (91.4%)
Headache	187 (34.4%)	146 (26.6%)
Nasopharyngitis	100 (18.3%)	98 (17.9%)
Pyrexia	76 (14.0%)	27 (4.9%)
Nausea	58 (10.7%)	43 (7.8%)
Lymphopenia	53 (9.8%)	6 (1.1%)
Back pain	51 (9.4%)	53 (9.7%)
Lymphocyte count decreased	49 (9.0%)	10 (1.8%)
Chills	44 (8.1%)	4 (0.7%)
Diarrhea	44 (8.1%)	58 (10.6%)
Abdominal pain	43 (7.9%)	21 (3.8%)
Respiratory tract infection	42 (7.7%)	38 (6.9%)
Respiratory tract infection viral	42 (7.7%)	31 (5.7%)
Upper respiratory tract infection	41 (7.6%)	38 (6.9%)
Influenza like illness	39 (7.2%)	11 (2.0%)
Insomnia	33 (6.1%)	16 (2.9%)
Pharyngitis	32 (5.9%)	12 (2.2%)
Pain in extremity	31 (5.7%)	24 (4.4%)
Oropharyngeal pain	31 (5.7)	19 (3.5)
Hyperthermia	31 (5.7)	6 (1.1)
Fatigue	28 (5.1)	20 (3.6)
Infusion related reaction	27 (5.0)	3 (0.5)

Source: Clinical Safety Review, Table 96

This table demonstrates that the overall rates of TEAEs were generally balanced between both treatment arms with approximately 90% of patients reporting a TEAE in the trial. The most common TEAE in both arms was headache, which is a common adverse event in any clinical trial and typically is reported in many patients regardless of treatment, as is the case here. Infections and infection-related symptoms such as pyrexia were common TEAEs associated with both treatments but were generally more commonly reported by subjects treated with ublituximab-xiiy. These higher rates of symptoms such as pyrexia, hyperthermia, and chills are also a

consequence of a high rate of infusion-related reactions associated with ublituximab-xiiy as discussed below.

Adverse Events of Special Interest and Special Safety Concerns

Refer to Dr. Baldassari's review for a comprehensive safety analysis of all adverse events. The summary below examines the key safety issues identified in this application.

Serious Infections

Infections were among the most common adverse events in the two controlled clinical trials in subjects with MS, with pneumonia representing the most common serious adverse event in these trials. Ublituximab-xiiy is a potent immune suppressant; ublituximab-xiiy treatment therefore is expected to confer an increased risk of infections even in comparison to an active comparator which is itself an immune suppressant. There were three deaths, all due to infections, in the blinded clinical trials, all occurring in ublituximab-xiiy exposed subjects. Serious, and fatal, infections have occurred with the other approved anti-CD20 therapies. Briumvi' s labeling will advise prescribers and subjects of the potential for serious potentially fatal infections as it does for other approved therapies in this class. Enhanced pharmacovigilance will also be requested for serious infections to identify risks in postmarketing that were not noted in the clinical trials.

A risk of hepatitis B reactivation has been identified in other anti-CD20 therapies. The clinical review notes that there were several cases of reactivated hepatitis B in subjects treated with ublituximab-xiiy in Studies RMS301 and RMS302. Therefore, labeling for Briumvi will include similar language to other anti-CD20 therapies regarding the appropriate pre-treatment testing and warning of risk necessary for the safe use of Briumvi.

The risk of progressive multifocal leukoencephalopathy (PML), identified with other immunosuppressants approved to treat MS, should be included among the labeling risks for Briumvi. PML is a serious potentially serious, potentially fatal, opportunistic infection. PML is an identified risk associated with the use of other anti-CD20 treatments (ocrelizumab and ofatumumab) approved for the treatment of MS, and therefore a significant potential exists for PML occurring with chronic use of Briumvi given its similar mechanism of action.

In summary, the observed and expected risks of serious and opportunistic infections associated with ublituximab-xiiy appear similar to the rates associated with other approved therapies for relapsing forms of MS. The safety database findings with

regard to the risk of serious infections with ublituximab-xiiy do not preclude approval.

Infusion-related Reactions

Infusion-related reactions are a known risk associated with monoclonal antibodies, and infusion-related reactions (a protocol-defined list of symptoms associated with hypersensitivity reactions) were therefore included as an adverse event of special interest in Studies RMS301 and RMS302. The protocols for these Phase 3 trials required premedication with an oral antihistamine (diphenhydramine 50 mg) and an oral corticosteroid (dexamethasone 10-20 mg). This is the same regimen used as pre-infusion prophylaxis for the approved intravenous anti-CD20 therapies; based on previous experience, this regimen does appear to reduce the frequency and severity of infusion-related reactions associated with anti-CD20 monoclonal antibody treatments.

The clinical review notes that infusion-related reactions were experienced by nearly half (47.7%) of subjects treated with ublituximab-xiiy as compared to 12.2% of sham-infused patients treated with teriflunomide. For comparison, Ocrevus labeling states that "34-40%" of subjects experienced an infusion-related reaction so the finding of 47.7% for ublituximab-xiiy is numerically higher but consistent with this rate for an approved therapy. All but a few infusion-related reactions were mild in severity; serious infusion-related reactions occurred in 0.7% of subjects infused with ublituximab-xiiy. There were no fatal infusion-related reactions. Many (43.3%) infusion-related reactions occurred with the initial infusion, and the rate of infusion-related reactions diminished with each subsequent infusion, with fewer than 5% of subjects experiencing any infusion-related reactions with the 5th infusion of ublituximab-xiiy. Based on the applicant's analysis of infusion-related reactions confirmed by the clinical reviewer, the low frequency, mild severity, and timing (i.e., hours after infusion completion when patients would not be in the infusion center) of the reactions experienced after the initial two doses of ublituximab-xiiy indicate that post-infusion observation after the initial two doses is only necessary for subjects who have a history of infusion-relate reactions and are not needed for all subjects. Labeling will describe the pre-treatment regimen, and the relevant data regarding infusion-related reactions, to inform providers and subjects of the information needed to safely administer Briumvi.

Immunoglobulin Reductions

In other anti-CD20 monoclonal antibody therapies, there is an observed progressive reduction in immunoglobulins, specifically immunoglobulins G and M, which appeared to confer a risk of serious infections additive to the initially observed risk of

serious infection associated with treatment. This risk is seen with prolonged use of anti-CD20 therapy and may be related to depletion of immunoglobulin production by mature B-cells. Though the overall rate of occurrence was low (0.7%) in both controlled trials, the only subjects who experienced TEASs related to reduced immunoglobulins were ublituximab-xiiy exposed subjects. Therefore, as is the case with other anti-CD20 therapies approved to treat MS, labeling for Briumvi will advise monitoring of immunoglobulins G and M and advise of a risk of infection with reduced immunoglobulin serum levels.

Fetal Toxicity

Nonclinical studies in primates suggested that there were fetal abnormalities that could reflect a direct toxicity of ublituximab-xiiy on the developing fetus (See Section 4). The fetal abnormalities associated with ublituximab-xiiy had not been observed in the nonclinical studies of ocrelizumab and ofatumumab. The clinical review noted that there were many safeguards to prevent pregnancy in the clinical trials, and that only nine pregnancies occurred in the Phase 3 studies. Of these nine pregnancies, four resulted in healthy-full-term infants. There were three elective abortions, and there were two pregnancies occurred with unknown outcomes due to subject withdrawal of consent. The unusual nature of the nonclinical findings, because monoclonal antibodies are not expected to exert transplacental developmental effects and because these findings were not seen in other similar therapies' nonclinical programs, led to the applicant proposing a Warning and Precaution for fetal toxicity which the review team agreed was appropriate. Overall, the reviewers across multiple disciplines including the Division of Risk Management concluded that nonclinical and human data did not appear to justify a risk evaluation and mitigation strategy (REMS) nor a boxed warning prohibiting use of Briumvi in pregnancy. However, given the potential for fetal toxicity, in addition to language promoting to use of effective contraceptive methods, labeling will require pregnancy testing before administration of Briumvi. The nonclinical team concluded that, due to technical limitations, further animal testing was not likely to provide interpretable findings to inform pregnancy-related components of labeling. There will be two postmarketing pregnancy studies (see Section 13,) and the Division is requesting enhanced pharmacovigilance for pregnancy complications to characterize the potential fetal effects of Briumvi in humans.

Hepatoxicity

Analysis of the safety database for ublituximab-xiiy generated an unexpected finding of increased reports of hepatobiliary dysfunction (2.4% of subjects treated with ublituximab-xiiy versus 2.2% of teriflunomide-treated subjects.) Since monoclonal antibodies such as ublituximab-xiiy are degraded in nonspecific protease pathways

and do not directly interact with liver metabolic degradative pathways, and because teriflunomide has a well-established potentially serious hepatotoxicity signal, this finding was unexpected. The overall observed rate of transaminase elevation was more than double for ublituximab-xiiy (1.3%) that of teriflunomide (0.5%). While teriflunomide was associated with an expected higher rate of increased alanine aminotransferase (4.7%), ublituximab-xiiy had a 3.9% overall rate of elevated alanine aminotransferase. Furthermore, ublituximab-xiiy exposure was associated with a 4.4% rate of aspartate aminotransferase elevation as compared to 1.8% in teriflunomide. There is no obvious explanation for these high rates of hepatic transaminase elevations in association with ublituximab-xiiy treatment. Monoclonal antibodies do not typically have rates of transaminase elevations approximate to teriflunomide's expected hepatic transaminase signal. The findings are not explained by hepatitis virus infection or reactivation because when hepatitis cases were excluded from this analysis, the discrepancy remained. There were no Hy's law cases, no cases of liver failure, and a consultant review by the Agency's drug-induced liver injury team concluded that while there were some similarities in overall adverse event rates, the transaminase data did not support a conclusion that ublituximab-xiiy was directly hepatotoxic. Enhanced pharmacovigilance will be requested to monitor for this potential safety signal.

Safety Conclusions

Ublituximab-xiiy is associated with adverse reactions, some serious and potentially fatal, but the risks of most treatment-emergent events identified in the clinical trials undertaken in subjects with MS can be reduced through minimally invasive screening, monitoring, and mitigated by low-risk interventions or discontinuation of therapy.

The three deaths occurring during the Phase 3 trials due to infections attributable to ublituximab-xiiy treatment were a focus of the BLA review. While the clinical review notes that two of these infections were due to uncommon etiologies (i.e., salpingitis and disseminated measles, respectively), rare infections leading to serious outcomes, including death, have been reported with other anti-CD20 monoclonal antibody therapies, and are a known potential consequence of any immune suppression, iatrogenic or otherwise. The approved labeling for the anti-CD20 therapy rituximab (not approved for MS, but often used off-label for this purpose) has been updated recently to provide additional language regarding the Warnings and Precautions of serious infections to reflect the emergence of post-marketing cases of rare infections with fatal outcomes. Similar updated language for the labeling for both Ocrevus and Kesimpta is actively being considered (a review of the relevant postmarketing cases

for these products by the Division of Pharmacovigilance [DPV] is ongoing, with the preliminary findings suggesting a similar risk).

Dr. Baldassari also found no difference in the overall incidences of TEAEs of infections or SAEs of infections with ublituximab-xiiy as compared to blinded trial data from other anti-CD20 therapies approved to treat MS. This finding further supports the similarity of ublituximab-xiiy with approved anti-CD20 monoclonal antibodies with respect to infection risk. Additionally, there is no mechanistic basis to believe that ublituximab-xiiy would differ from other approved anti-CD20 monoclonal antibodies with respect to immunosuppression leading to fatal infections because all of the members of this class of therapies selectively and rapidly deplete CD20 positive B-cells to the same extent; that is, almost all patients who receive these therapies have serum CD20-expressing B-cell counts below detection thresholds throughout treatment.

Ultimately, the infection-related deaths of three subjects in the Phase 3 blinded trials are not indicative of novel risks exclusive to ublituximab-xiiy because serious, including fatal, infections are associated with all approved anti-CD20 therapies based on postmarketing experience. Given the consistency with what is known about other drugs in this class, discussion of the infection-related safety findings with an Advisory Committee was not required, nor was there a scientific basis for an approach to labeling for ublituximab-xiiy that differed from other drugs in this class, such as a boxed warning or a second-line indication. Furthermore, the Division of Risk Management (DRM) concluded that a Risk Evaluation and Mitigation Strategy (REMS) was not necessary to ensure the safe use of ublituximab-xiiy. Labeling for Briumvi will describe these fatal cases from Studies RMS301 and RMS302 and otherwise will align with the contemporary Warning and Precautions language for a member of this class of therapies, which describes a potential for fatal infections.

Likewise, labeling for Briumvi will describe risks of specific infections such as PML and hepatitis B which have been identified as specific infection risks for other anti-CD20 therapies. The inclusion in labeling of a need to monitor immunoglobulins is consistent with emerging evidence that chronic long-term use of anti-CD20 monoclonal antibody therapies is associated with a clinically significant depletion of serum immunoglobulin pools and an additional increased risk of serious infection that emerges with chronic use. A postmarketing requirement to study immunoglobulins during long-term Briumvi therapy is being imposed to allow for further understanding of this serious safety issue. Pregnancy registry and outcomes studies are needed because Briumvi will be used in the MS population which is predominantly women of childbearing potential and data regarding pregnancy

outcomes are limited; there will be a warning for potential fetal toxicity due to nonclinical findings and enhanced observation for pregnancy complications. A postmarketing study of human milk exposure will also provide data concerning postnatal exposure effects and risks.

Even with several serious concerns regarding safety, Briumvi is a highly effective therapy and therefore can be approved even with proven or strongly suspected serious safety risks because these risks appear to be similar to those of other approved therapies in its class, and the disease that Briumvi is proposed to treat, MS, remains incurable, disabling, and possibly fatal.

9. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because this biologic is not the first in its class, the safety profile is similar to that of other biologics approved for this indication, the clinical trial designs are acceptable, and the application did not raise significant safety or efficacy issues that were unexpected for a biologic in this class.

10. Pediatrics

No clinical pediatric data were provided. An initial Pediatric Study Plan to study ublituximab-xiiy in subjects ages 10-17 years with relapsing forms of MS that was submitted by the applicant on May 21, 2021, as required by the Pediatric Research Equity Act (PREA). This submission was deemed acceptable. The PMR for a pediatric study is described in Section 11.

11. Other Regulatory Issues

This section may include discussion on other issues (if not addressed in previous sections):

- The Division of Medication Error Prevention and Analysis (DMEPA) conducted a review of the proprietary name, “Briumvi” and the suffix for ublituximab (“-xiiy”) and found that both were acceptable for use.

- The Division of Risk Management (DRM) review concluded that a REMS was not necessary. The DRM review stated that the Warning and Precaution for serious infections was sufficient to inform prescribers and patients of this potentially fatal treatment risk. The DRM review also agreed that the

embryofetal toxicity risk was adequately described in labeling, and that the data in the BLA did not support a boxed warning nor a need for a REMS for pregnancy.

- The Office of Scientific Investigations (OSI) review noted that OSI had conducted a For-Cause inspection of TG Therapeutics from January 19-29, 2021, in response to the Division's concerns regarding potential under-reporting and delayed submission of IND safety reports, specifically those reports related to serious infections. This inspection revealed that the applicant did not have a formalized standard operating procedure for assessing safety during the conduct of Studies RMS 301 and RMS302, and the absence of a routine procedure led to incomplete and delayed reporting. The inspectors also noted that the rationale for evaluating causality of safety reporting was unclear and appeared to rely entirely on investigator assessment of causality without a central review. At the time of the inspection, the applicant claimed to have implemented all changes to safety reporting requested by the DN2, including a reconsideration of causality in all prior safety reports, but the OSI team concluded that the applicant had only reassessed most, not all, prior safety reports. OSI and the Division concluded that the BLA contained all safety reporting in existence, regardless of causality, and therefore represented a complete safety database for review. It was determined that there was no need for an additional re-inspection of the applicant, and thus there was no inspection of the applicant as part of the BLA review.

  OSI conducted inspections for the BLA at four clinical sites. An inspection of a site in Belgrade, Serbia, directed by Dr. Evica Dinčić, revealed that several adverse events had not been reported to the applicant, most concerning being lymphopenia reported in three subjects randomized to ublituximab-xiiy. These events were added to the safety database but since lymphopenia was an event of special interest already identified with the class of therapies, these additional events did not change the overall safety evaluation. An inspection of a site in Zagreb, Croatia directed by Dr. Mario Habek identified concomitant medication use in six subjects which was not reported to the applicant. These concomitant medications were used to treat minor medical conditions unrelated to investigational treatments. The addition of these medications and minor adverse events did not change the safety analysis conclusions. An inspection of a site in Tampa, Florida, USA, directed by Dr. Derrick Robinson uncovered no significant issues. Finally, an inspection of a clinical site in Knoxville, TN, USA, under the direction of Dr. Sibyl Wray, revealed that unblinded MRI results for three subjects had been shared with the site and had

been reviewed by Dr. Wray in violation of the trials' protocols that only blinded safety information should be shared with sites and investigators except when necessary for safety. A corrective action plan had been implemented by the applicant at this site after these unblinding events had occurred. The Division requested a comprehensive review of all unblinded MRI information sharing which revealed 12 protocol violations in nine subjects from Study RMS301 and 16 protocol violations in seven subjects from Study RMS302. All of these violations had been disclosed previously in the BLA submission as protocol violations and appeared to be attributable to a lack of training of study personnel. Exclusion of these subjects' data in exploratory sensitivity analyses of the primary efficacy outcome measure revealed no effect on the significance of the ARR findings and did not change conclusions regarding the overall efficacy findings in these trials.

12. Labeling

See the final negotiated product label. Labeling negotiations with the applicant have been completed, and the applicant has accepted all recommended changes.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

A REMS is not necessary for Briumvi (ublituximab-xiiy).

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following are postmarketing requirements:

1. Conduct a two-part study of Briumvi (ublituximab-xiiy) in pediatric patients with relapsing forms of multiple sclerosis (RMS) at least 10 years and less than 18 years of age. Part A is an open-label study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of Briumvi (ublituximab-xiiy) in pediatric patients. Part A will include two cohorts, one with body weights less than 40 kg and the other with body weights 40 kg or more. The objective of Part A is to determine maintenance doses of Briumvi (ublituximab-xiiy) that will result in PK and PD effects that are comparable to those of the dose administered to adult patients. Part B is a randomized, blinded, non-inferiority trial with Gilenya (fingolimod) as a comparator.

Draft Protocol Submission:	06/2024
Final Protocol Submission:	01/2025
Study Completion:	01/2030
Final Report Submission:	09/2030

2. Provide an assessment of the potential for Briumvi (ublituximab-xiiy) to have adverse effects on immune function when administered to animals during the postnatal period.

Draft Protocol Submission:	01/2025
Final Protocol Submission:	12/2025
Study Completion:	01/2028
Final Report Submission:	09/2028

3. 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-xiiy) during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to Briumvi (ublituximab-xiiy) 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.

Draft Protocol Submission:	07/2023
Final Protocol Submission:	03/2024
Annual Interim Report Submissions:	03/2025
	03/2026
	03/2027
	03/2028
	03/2029
	03/2030
	03/2031
	03/2032
	03/2033
	03/2034

Study Completion:	03/2035
Final Report Submission:	03/2036

4. 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
	03/2026
	03/2027
	03/2028
	03/2029
	03/2030
	03/2031
	03/2032
	03/2033
	03/2034
Study Completion:	03/2035
Final Report Submission:	03/2036

5. A safety trial to monitor serum immunoglobulin G and M levels in patients with relapsing forms of multiple sclerosis during treatment with Briumvi (ublituximab-xiiy) to establish the nadir in circulating immunoglobulins during chronic treatment, and to monitor patients after discontinuation of treatment with Briumvi (ublituximab-xiiy) in order to ascertain the time needed to ensure restoration of pretreatment baseline circulating serum levels of immunoglobulins G and M. This trial also should be designed to capture rates of infections, especially opportunistic and recurrent infections associated with immune suppression, and there should be monitoring of B-cell counts throughout treatment and after discontinuation until repletion of immunoglobulin levels.

Draft Protocol Submission:	06/2023
Final Protocol Submission:	02/2024

Trial Completion:	06/2030
Final Report Submission:	06/2031

6. Perform a lactation study (milk only) in lactating women who have received therapeutic doses of Briumvi (ublituximab-xiiy) using a validated assay to assess concentrations of Briumvi (ublituximab-xiiy) in breast milk and the effects on the breastfed infant.

Draft Protocol Submission:	07/2023
Final Protocol:	03/2024
Study Completion:	06/2025
Final Report Submission:	01/2026

The following are postmarketing commitments:

1. To optimize the antibody-dependent cellular cytotoxicity (ADCC) Potency Assay with the goal of reducing method variability as well as implement a comprehensive and robust control strategy to control ADCC activity of ublituximab drug substance and drug product at release and stability, and to submit the proposed relevant specifications as a Prior Approval Supplement in accordance with 21 CFR 601.12 (b).

   Final Report Submission: 12/2023

2. To implement and validate an analytical method to control polysorbate 80 concentration for ublituximab drug product at release and stability.

   Final Report Submission: 03/2023

3. To establish an ublituximab working reference standard (WRS) and submit WRS qualification data for the first WRS as well as a WRS requalification protocol.

   Final Report Submission: 01/2023

4. To develop a neutralization assay and submit a full validation report of the newly developed neutralization assay, re-analyze neutralizing antibody in patients enrolled in the pivotal clinical studies (TG1101-RMS301 and TG1101-RMS302), and evaluate the potential impact on the pharmacokinetics, pharmacodynamics, safety and efficacy of ublituximab.

Final Report Submission: 08/2024

14. Recommended Comments to the Applicant

There are no additional recommended comments for the applicant.

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.

/s/

PAUL R LEE
12/28/2022 10:39:17 AM

WILLIAM H Dunn
12/28/2022 11:07:30 AM