BLA 761238

BLA APPROVAL

TG Therapeutics, Inc.
Attention: Hari Miskin, Chief Development Officer
3020 Carrington Mill Blvd, Suite 475
Morrisville, NC 27560

Dear Mr. Miskin:

Please refer to your biologics license application (BLA) dated and received September 28, 2021, and your amendments, submitted under section 351(a) of the Public Health Service Act for Briumvi (ublituximab-xiiy) injection for intravenous use.

We acknowledge receipt of your major amendments dated March 31, 2022, and April 5, 2022, which extended the goal date by three months.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2090 to TG Therapeutics, Inc., Morrisville, North Carolina, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Briumvi (ublituximab-xiiy). Briumvi is indicated for the treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ublituximab-xiiy drug substance and final formulated drug product at Samsung Biologics Co., Ltd., in Yeonsu-gu, Incheon, Republic of Korea. The final formulated drug product will be labeled and packaged at Packaging Coordinators, LLC, Philadelphia, PA, USA. You may label your product with the proprietary name, Briumvi, and market it in a 150 mg/6 mL solution.

DATING PERIOD

The dating period for Briumvi shall be 24 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of final sterile

filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) from the date of manufacture when stored at (b) (4)

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Briumvi (ublituximab-xiiy) to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Briumvi (ublituximab-xiiy), or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with the minor editorial revision of the addition of “2090” to replace the placeholder as the U.S. License No. in the Prescribing Information and Medication Guide, which is reflected in the enclosed labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[2]

[1] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on September 16, 2022, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761238**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Briumvi (ublituximab-xiiy) 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.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to less than 10 years because necessary studies are impossible or highly impracticable. This waiver is being granted because the number of children diagnosed with relapsing forms of multiple sclerosis in that age group is small.

We are deferring submission of your pediatric studies for ages 10 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

4337-1 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

4337-2 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

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 127265 with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Briumvi (ublituximab-xiiy) during pregnancy, or to identify an unexpected serious risk of the potential presence of Briumvi (ublituximab-xiiy) in human breast milk resulting in effects on the breastfed infant.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4337-3 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.

The timetable you submitted on November 4, 2022, states that you will conduct this study according to the following schedule:

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

4337-4 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.

The timetable you submitted on December 6, 2022, states that you will conduct this study according to the following schedule:

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

4337-5 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.

The timetable you submitted on November 21, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2023
Final Protocol Submission:	03/2024

Study Completion:	06/2025
Final Report Submission:	01/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of diminished serum immunoglobulin levels and the potential for a resultant increased risk of infections, particularly opportunistic infections.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4337-6 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.

The timetable you submitted on November 4, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2023
Final Protocol Submission:	02/2024
Trial Completion:	06/2030
Final Report Submission:	06/2031

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[5] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submit clinical protocol(s) to your IND 127265 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o)**.

Submission of the protocols for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4337-7 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-xiiy 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).

The timetable you submitted on June 1, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2023

4337-8 To implement and validate an analytical method to control polysorbate 80 concentration for ublituximab-xiiy drug product at release and stability.

The timetable you submitted on June 1, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2023

4337-9 To establish a ublituximab-xiiy working reference standard (WRS) and submit WRS qualification data for the first WRS as well as a WRS requalification protocol.

The timetable you submitted on August 18, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2023

4337-10 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-xiiy.

The timetable you submitted on August 18, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2024

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance and enhanced pharmacovigilance for malignancy, immune-mediated colitis, serious/opportunistic infections (including hepatitis B, progressive multifocal leukoencephalopathy, and central nervous system infections), hepatotoxicity/hepatic disorders independent of hepatitis B, pancreatitis, thrombocytopenia, and pregnancy complications. Report all confirmed or possible cases to the BLA in an expedited fashion and include comprehensive summaries for these events as part of your required postmarketing safety reports (e.g., periodic safety update reports [PSURs]). We additionally request

that you summarize reports of pregnancy exposures and maternal and fetal outcomes as part of your required postmarketing safety reports.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[6]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[7] Information and Instructions for completing the form can be found at FDA.gov.[8]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements at 21 CFR 600.81.

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding, and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

[6] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[8] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, please contact Rania Younes, Senior Regulatory Project Manager, by email at rania.younes@fda.hhs.gov or by phone at (301) 837-7347.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

WILLIAM H Dunn
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