BLA 761164

BLA APPROVAL

Bioverativ USA Inc.
Attention: Amanda Meisel, PharmD, RPh
US Lead, North America Rare and Rare Blood Disorders
55 Corporate Drive
Bridgewater, NJ 08807

Dear Dr. Meisel:

Please refer to your biologics license application (BLA) dated and received March 13, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Enjaymo (sutimlimab-jome) injection.

We acknowledge receipt of your resubmission dated August 5, 2021, which constituted a complete response to our November 13, 2020, action letter.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2078 to Bioverativ USA Inc., Waltham, MA, 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 Enjaymo (sutimlimab-jome). Enjaymo is indicated to decrease the need for red blood cell (RBC) transfusion due to hemolysis in adults with cold agglutinin disease (CAD).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture sutimlimab drug substance at (b) (4). The final formulated drug product will be manufactured and filled at (b) (4). The final formulated drug product will be labeled and packaged at Sanofi Genzyme Northborough, Northborough, Massachusetts, and Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany. You may label your product with the proprietary name, Enjaymo, and market it in 1100 mg/22 mL solution.

DATING PERIOD

The dating period for Enjaymo shall be 18 months from the date of manufacture when stored at 2°C to 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) months 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 periods 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 Enjaymo 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 Enjaymo, 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.

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

[1] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[2]

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 enclosed carton and container labeling submitted on November 16, 2021, (carton labeling) and December 10, 2021, (container labeling), 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 Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. For administrative purposes, designate this submission "Final Printed Carton and Container Labeling for approved BLA 761164." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for sutimlimab was not referred to an FDA advisory committee because evaluation of the submitted data did not raise significant safety or efficacy issues that warranted public discussion.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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.

[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.

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 assess a signal of the risk of development of new or worsening autoimmune diseases and the risk of serious infections, especially those caused by encapsulated bacteria. 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 risk(s).

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

3922-1 Conduct a 5-year registry study to characterize the safety of sutimlimab in patients with primary Cold Agglutinin Disease. Yearly interim reports and the final study report should include a summary of the major safety findings and outcome of events. The summaries must discuss available information on autoimmune diseases, serious bacterial infections, sutimlimab dosing, vaccination status, serotype/serogroup of Streptococcus pneumoniae and Neisseria meningitidis isolates, and concomitant medications.

The timetable you submitted on January 28, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 09/2022
Final Protocol Submission: 04/2023
Annual Interim Report #1: 08/2024
Annual Interim Report #2: 08/2025
Annual Interim Report #3: 08/2026
Annual Interim Report #4: 08/2027
Annual Interim Report #5: 08/2028
Annual Interim Report #6: 08/2029
Annual Interim Report #7: 08/2030
Final Report Submission: 10/2031

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.[3]

3922-2 Complete part B of study BIVV009-03, “A Phase 3, Pivotal, Open-Label, Multicenter Study to Assess the Efficacy and Safety of BIVV009 in Patients with Primary Cold Agglutinin Disease Who Have a Recent History of Blood Transfusion “. Include updated summary safety and efficacy

[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.

analysis and submit datasets at the time of final clinical study report submission.

The timetable you submitted on January 28, 2022, states that you will conduct this trial according to the following schedule:

Final Report Submission: 08/2022

3922-3 Complete part E of study BIVV009-01, "Safety, Tolerability and activity of TNT009 in Healthy Volunteers and Patient with Complement-Mediated Disorders. A Single/Multiple Ascending Dose Phase 1 Study". Include updated summary safety and efficacy analysis in the final clinical study report.

The timetable you submitted on January 28, 2022, states that you will conduct this trial according to the following schedule:

Final Report Submission: 08/2022

3922-4 Complete Part B of Study BIVV009-04, "A Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of BIVV009 in patients with primary Cold Agglutinin Disease without a recent history of blood transfusion". Include updated safety information and submit datasets at the time of final clinical study report submission.

The timetable you submitted on January 28, 2022, states that you will conduct this trial according to the following schedule:

Final Report Submission: 08/2022

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]
Submit clinical protocol(s) to your IND 128190 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).**

[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.

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.

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*.[5]

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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (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 for licensed biological products (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.

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

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:

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, contact Maureen DeMar, BSN, RN, Regulatory Project Manager, at 240-402-9981 or at Maureen.DeMar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, MD
Deputy Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

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/

LISA B YANOFF
02/04/2022 12:57:59 PM