BLA 761309

BLA ACCELERATED APPROVAL

Genentech, Inc.
c/o Hoffmann-La Roche Inc.
Attention: Steven Barrett, PhD
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Barrett:

Please refer to your biologics license application (BLA) dated and received November 1, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Columvi (glofitamab-gxbm) injection.

LICENSING

We have approved your BLA for Columvi (glofitamab-gxbm) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Columvi under your existing Department of Health and Human Services U.S. License No. 1048. Columvi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Columvi (glofitamab-gxbm) drug substance at Roche Diagnostics GmbH, Penzberg, Germany. The final formulated product will be manufactured and filled at Genentech, Inc., San Francisco, California and labeled, secondary packaged, and stored at F. Hoffman-La Roche AG, Wurmisweg 4303 Kaiseraugst, Switzerland. You may label your product with the proprietary name Columvi and will market it in 2.5 mg/2.5 mL single-dose vial and in 10 mg/10 mL single-dose vial.

DATING PERIOD

The dating period for Columvi shall be 24 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) (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.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Columvi and each kit component 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 Columvi, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 601.41, effective on the date of this letter, for use as recommended in the enclosed agreed-upon approved labeling. This BLA provides for the use of Columvi for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapy.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

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, as described at FDA.gov.[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 draft 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.

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

[2] When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and 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 (February 2020, Revision 7)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761309**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for glofitamab-gxbm was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct further adequate and well-controlled clinical trial intended to verify and describe clinical benefit. You are required to conduct such clinical trial with due diligence. If required postmarketing clinical trial fails to verify clinical benefit or is not conducted with due diligence, including with respect to the conditions set forth below, we may, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated June 6, 2023. This requirement is listed below.

4464-1 Complete a randomized clinical trial that evaluates the clinical benefit of glofitamab in patients with diffuse large B-cell lymphoma. The trial should compare glofitamab in combination with gemcitabine and oxaliplatin (GemOx) to rituximab in combination with GemOx for patients with relapsed or refractory diffuse large B-cell lymphoma. The primary endpoint should be overall survival with secondary endpoints that include progression-free survival and response rate.

The timetable you submitted on June 6, 2023, states that you will conduct this trial according to the following schedule:

Trial Completion:	03/2024
Final Report Submission:	09/2024

Submit clinical protocols to your IND 138178 for this product. 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.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this BLA not later than 180 days after the date of approval of this BLA and every 180 days thereafter (per section 506B(a)(2) of the FDCA). The report should include:

- expected trial completion and final report submission dates
- any changes in plans since the last report with rationale for any changes
- the current number of patients entered into each trial

Reports submitted 180 days after the date of approval of this BLA and on such date each year thereafter must be clearly designated "[180-Day AA PMR Progress Report]."

Reports submitted one year after the date of approval of this BLA and on such date each year thereafter may be submitted as part of your annual status report required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. FDA will consider the submission of your annual status report under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval and on such date each year thereafter, to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

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 <6 months because necessary studies are impossible or highly impracticable. This is because of the rarity of pediatric patients ages <6 months with mature B-cell non-Hodgkin lymphoma.

We are deferring submission of your pediatric study for ages 6 months or older for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

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

4464-2 Conduct a study assessing the efficacy and safety of glofitamab in pediatric patients 6 months or older with relapsed or refractory non-Hodgkin lymphoma. The safety endpoints should evaluate safety and tolerability of glofitamab monotherapy and in combination with standard chemotherapy and identify the recommended dosage. The efficacy endpoints should evaluate activity as assessed by response rate and durability of response.

The timetable you submitted on June 6, 2023, states that you will conduct this study according to the following schedule:

Study Completion:	12/2027
Final Report Submission:	06/2028

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 138178, 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4464-3 Conduct an integrated analysis of data from clinical trials to further characterize the safety, efficacy, pharmacokinetics, and pharmacodynamics of glofitamab among U.S. racial and ethnic minority patients with large B-cell lymphoma. The population should be representative of the U.S. population of patients with large B-cell lymphoma, including racial and ethnic diversity, and allow for interpretation of the results in these populations.

The timetable you submitted on June 6, 2023, states that you will conduct this study according to the following schedule:

[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.

Draft Protocol Submission:	12/2023
Final Protocol Submission:	06/2024
Study Completion:	06/2027
Final Report Submission:	12/2027

4464-4 Conduct an analysis of duration of response with extended follow-up in patients with diffuse large B-cell lymphoma or transformed follicular lymphoma who discontinue glofitamab monotherapy after receiving 12 cycles. Provide this additional duration of response data, as assessed by an IRC, in patients in the primary efficacy population of Study NP30179, with a targeted minimum of one year of extended follow-up after completion of 12 cycles of glofitamab. Include data regarding new anti-lymphoma therapy and efficacy outcomes after glofitamab retreatment.

The timetable you submitted on June 6, 2023, states that you will conduct this study according to the following schedule:

Trial Completion:	05/2024
Final Report Submission:	11/2024

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 138178 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70, you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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*.[4]

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. 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

[4] https://www.fda.gov/media/128163/download

New molecular entities and new biologics 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, call Laura Wall, Senior Regulatory Project Manager, at 301-796-2237.

Sincerely,

{See appended electronic signature page}

Marc Theoret, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
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/

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