CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761324Orig1s000

Trade Name:	Epkinly
Generic or Proper Name:	epcoritamab-bysp
Sponsor:	Genmab US, Inc.
Approval Date:	May 19, 2023
Indication:	For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B cell lymphoma after two or more lines of systemic therapy

CENTER FOR DRUG EVALUATION AND RESEARCH

216951Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

BLA 761324

BLA ACCELERATED APPROVAL

Genmab US, Inc.
Attention: Donghui Ni
Director, Regulatory Affairs
777 Scudders Mill Road
Bldg. 2, 4th Floor
Plainsboro, NJ 08536

Dear Mr. Ni:

Please refer to your biologics license application (BLA) dated and received September 21, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Epkinly (epcoritamab-bysp) injection.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2293 to Genmab US, Inc., Plainsboro, New Jersey, 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 Epkinly (epcoritamab-bysp). Epkinly is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B cell lymphoma after two or more lines of systemic therapy.

Under this license, you are approved to manufacture (b) (4) the epcoritamab drug substance at (b) (4) (b) (4) The final formulated product will be manufactured and filled at (b) (4) (b) (4) and labeled and packaged at (b) (4) You may label your product with the proprietary name Epkinly and will market it as 4 mg/0.8 mL (5 mg/mL) and 48 mg/0.8 mL (60 mg/mL) in a single-dose vial.

DATING PERIOD

The dating period for Epkinly 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) °C. (b) (4)

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your (b) (4) (b) (4) epcoritamab 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 Epkinly 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 Epkinly, 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 Epkinly for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell 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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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.

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 761324**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for epcoritamab-bysp was not referred to an FDA advisory committee because it did not raise significant safety or efficacy issues.

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 trials intended to verify and describe clinical benefit. You are required to conduct such clinical trial(s) with due diligence. If required postmarketing clinical trial(s) fail to verify clinical benefit or are not

[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.

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(s) specified in your submission dated May 9, 2023. This requirement is listed below.

4435-1 Complete a randomized clinical trial in patients with relapsed or refractory large B-cell lymphoma. The trial should compare epcoritamab monotherapy to an investigator's choice of standard therapies for patients with relapsed or refractory 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 May 9, 2023, states that you will conduct this trial according to the following schedule:

Trial Completion:	12/2024
Final Report Submission:	06/2025

Submit clinical protocols to your IND 135659 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 <1 year because necessary studies are impossible or highly impracticable. This is because of the extremely low prevalence of mature B cell lymphoma in this age group

We are deferring submission of your pediatric study for ages ≥1 to 18 years 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.

4435-2 Complete a clinical trial to confirm the appropriate dose of epcoritamab and to assess the safety, pharmacokinetics, and preliminary efficacy of epcoritamab monotherapy in pediatric patients with relapsed or refractory aggressive mature B-cell lymphoma.

Trial Completion: 11/2028
Final Report Submission: 05/2029

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 135659, 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 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 assess known serious risks of immune effector cell-associated neurotoxicity syndrome, neurologic toxicity, hematologic adverse events, and infections.

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.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

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

4435-3 Conduct an integrated safety analysis of data from patients with large B-cell lymphoma and other lymphoid malignancies to further characterize the long-term incidence, severity, and outcome of the known serious risks of immune effector cell-associated neurotoxicity syndrome, neurologic toxicity, hematologic adverse events, and infections. Include a comprehensive analysis from all available data sources including but not limited to patient-level and pooled analyses of ongoing and completed clinical trials.

The timetable you submitted on May 9, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission (Analysis Plan):	12/2024
Final Protocol Submission (Analysis Plan):	12/2025
Interim Report Submission:	12/2026
Trial Completion:	05/2028
Final Report Submission:	11/2028

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.

Submit clinical protocol(s) to your IND 135659 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).**

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(a)(1) 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(a)(1) 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 SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4435-4 Conduct an integrated analysis of data from clinical trials to further characterize the safety, efficacy, pharmacokinetics, and pharmacodynamics of epcoritamab monotherapy among U.S. racial and ethnic minority patients with large B-cell lymphoma. The population should be representative of the U.S. population, including racial and ethnic diversity, of patients with large B-cell lymphoma and allow for interpretation of the results in these populations.

The timetable you submitted on May 9, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Analysis Plan):	06/2024
Final Protocol Submission (Analysis Plan):	06/2025
Study Completion:	02/2028
Final Report Submission:	08/2028

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

We remind you of your postmarketing commitments:

4435-5 Develop and validate an assay to evaluate the neutralizing capacity of epcoritamab anti-drug-antibodies (ADAs) detected in the patient samples by end of Q3 2023. The assay should be capable of sensitively detecting neutralizing ADAs in the presence of epcoritamab levels that are expected to be present in serum at the time of patient sampling. The final report should include assay validation report and assay standard operating procedure (SOP).

The timetable you submitted on April 05, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2023

4435-6 Develop, validate, and implement a CIEX-HPLC method for release and stability testing of epcoritamab drug substance and drug product in addition to the existing icIEF method for charge heterogeneity. Submit the method validation report and update the epcoritamab drug substance and drug product specifications and other relevant BLA sections.

The timetable you submitted on April 05, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2023

4435-7 Conduct additional validation study to support linearity, range, and accuracy of the A280 protein concentration method using representative epcoritamab (b) (4) drug substance and drug product samples. In addition, Genmab should conduct additional validation study to support the range and accuracy of the protein assay (b) (4) (b) (4) to support suitability of the method at this site. Submit the method validation report and update the relevant BLA sections of the epcoritamab drug substance and drug product.

The timetable you submitted on April 05, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2023

4435-8 Re-evaluate and update the acceptance criteria for biological activity of both epcoritamab drug substance and drug products after 10 additional commercial drug product batches have been released. Submit the reanalysis final report and update the epcoritamab drug substance and drug product specifications and other relevant BLA sections.

The timetable you submitted on April 05, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

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 135659 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

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.

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

If you have any questions, call Natasha Kormanik, Senior Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Marc R. 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/

MARC R THEORET
05/19/2023 11:30:21 AM