CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761324Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 05/03/2023

To: Natasha Kormanik, MSN, CRNP, FNP-BC, OCN
Senior Regulatory Health Project Manager
Division of Hematological Malignancies II (DHM2)

From: Louiza Bako, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for EPKINLY (epcoritamab-bysp) injection, for subcutaneous use

BLA: 761324

Background:
In response to DHM2's consult request dated October 12, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for the original BLA submission for EPKINLY (epcoritamab-bysp) injection, for subcutaneous use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 19, 2023, and our comments are provided below.

Medication Guide:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on April 28, 2023.

Thank you for your consult. If you have any questions, please contact Louiza Bako at (b) (6) (b) (6) or Louiza.Bako@fda.hhs.gov.

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/s/

LOUIZA N BAKO
05/03/2023 09:48:39 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 1, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761324
Product Name, Dosage Form, and Strength:	Epkinly (epcoritamab- bysp) Injection, 4 mg/0.8 mL, 48 mg/0.8 mL
Applicant/Sponsor Name:	Genmab US, Inc.
TTT ID #:	2022-1759-2
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 27, 2023 for Epkinly. We reviewed the revised container labels and carton labeling for Epkinly (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Iverson, N. Label and Labeling Review for Epkinly (BLA 761324). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 APR 20. TTT ID No.: 2022-1759-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 27, 2023

Container labels

(b) (4)

Carton labeling

(b) (4)

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/s/

NICOLE F IVERSON
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HINA S MEHTA
05/01/2023 05:59:50 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 28, 2023
To:	Natasha Kormanik, MSN, CRNP, FNP-BC, OCN® Senior Regulatory Health Project Manager **Division of Hematologic Malignancies II (DHM2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Louiza Bako, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	EPKINLY (epcoritamab-bysp)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761324
Applicant:	Genmab US, Inc.

1 INTRODUCTION

On September 21, 2022, Genmab US, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761324 for EPKINLY (epcoritamab-bysp) injection, with a proposed indication (b) (4) [redacted]

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies II (DHM2) on October 12, 2022 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for EPKINLY (epcoritamab-bysp) injection.

2 MATERIAL REVIEWED

- Draft EPKINLY (epcoritamab-bysp) injection MG received on September 21, 2022, and received by DMPP and OPDP on April 19, 2023.
- Draft EPKINLY (epcoritamab-bysp) injection Prescribing Information (PI) received on September 21, 2022 and received by DMPP and OPDP on April 19, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

JESSICA M CHUNG
04/28/2023 12:41:29 PM

LOUIZA N BAKO
04/28/2023 12:51:02 PM

SHARON R MILLS
04/28/2023 01:15:40 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 20, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761324
Product Name and Strength:	Epkinly (epcoritamab- bysp) Injection, 4 mg/0.8 mL, 48 mg/0.8 mL
Applicant/Sponsor Name:	Genmab US, Inc.
TTT ID #:	2022-1759-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on February 16, 2023 for Epkinly. We review the revised container labels and carton labeling for Epkinly (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. The nonproprietary name suffix is denoted by the placeholder "epcoritamab-xxxx". Additionally, there is inadequate (b) (4) (b) (4)

3 RECOMMENDATIONS FOR GENMAB US, INC.

[a] Iverson, N. Label and Labeling Review for Epkinly (BLA 761324). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 Feb 13.TTT ID: 2022-1759.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels and Carton labeling)
    1. As currently presented, the nonproprietary name suffix is denoted by the placeholder "epcoritamab-xxxx". Replace all presentations of the placeholder "epcoritamab-xxxx" with the conditionally acceptable nonproprietary name suffix, epcoritamab-bysp.

B. 48 mg/0.8 mL Carton Labeling
    1. (b) (4) Lack of adequate differentiation may contribute to product selection errors. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme. Revise (b) (4)

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 16, 2023

Container labels

(b) (4)

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HINA S MEHTA
04/22/2023 10:02:34 PM

CLINICAL INSPECTION SUMMARY

Date	3/29/2023
From	Leigh Marcus, M.D., Senior Physician Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Natasha Kormanik, Regulatory Project Manager Nicole Sunseri, M.D., Ph. D., Clinical Reviewer Nicholas Richardson, D.O., M.P.H., Team Leader Nicole Gormley, M.D., Division Director Division of Hematologic Malignancies 2 (DHM2) Office of Oncologic Diseases (OOD)
BLA #	761324
Applicant	Genmab US, Inc.
Drug	Epcoritamab
NME	Yes
Review Priority	Priority
Proposed Indication	(b) (4)
Consultation Request Date	11/1/2022
Summary Goal Date	3/28/2023
Updated Summary Goal Date	4/11/2023
Action Goal Date	5/14/2023
PDUFA Date	5/21/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study GCT3013-01 were submitted to the Agency in support of this Biologic License Application (BLA) for epcoritamab (b) (4)

Two clinical investigators (CIs): Drs. Yasmin Karimi (Site #US02) and Catherine Thieblemont (Site #FR07), as well as the sponsor, Genmab US, Inc., were inspected for Study GCT3013-01.

Based on the inspections of two CI and the sponsor, no significant regulatory violations were identified. The clinical data generated by these CI sites are verifiable. The sponsor's oversight and monitoring of Study GCT3013-01 were adequate. This study appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Epcoritamab administered by subcutaneous injection was being developed under IND (#135659) (b) (4) The sponsor has submitted the results of Study GCT3013-01, an open label, single-arm, dose-escalation and expansion trial, to support efficacy and safety for this indication.

Study GCT3013-01

Title: "A Phase 1/2, Open-Label, Dose-Escalation Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma"

Study GCT3013-01 was an open label, single-arm, dose-escalation and expansion trial in subjects with relapsed, progressive, and/or refractory CD20+ B-cell lymphoma who had received at least 2 prior therapy regimens. Study GCT3013-01 had 3 expansion cohorts.

The primary efficacy endpoint was overall response rate (ORR) in the Dose Expansion Part of the study, in which there were 3 disease cohorts initiated with parallel enrollment:

1. aggressive relapsed or refractory B-NHL ([aNHL]; i.e., LBCL)
2. indolent B-cell non-Hodgkin lymphoma (iNHL), and
3. mantle cell lymphoma (MCL).

The study was comprised of 3 periods: a screening and enrollment period, a study intervention period, and a post study follow up period. The proposed dosing regimen includes an initial priming dose of epcoritamab 0.16 mg on Cycle 1 Day 1, an intermediate dose of 0.8 mg on Cycle 1 Day 8, and a full dose of 48 mg on Cycle 1 Day 15, Cycle 1 Day 22, and thereafter. Epcoritamab was administered by subcutaneous injection in 28-day cycles, with weekly dosing in Cycles 1 to 3, every 2 weeks dosing in Cycles 4 to 9, and every 4 weeks dosing in Cycle 10 and beyond until unacceptable toxicity or disease progression. The primary efficacy endpoint of ORR was determined by Lugano criteria and assessed by independent review committee (IRC).

The trial was conducted in 54 sites in 13 countries. Study subjects first enrolled on June 26, 2018. Data cut-off calendar date for this application submission was January 31, 2022. The study was ongoing at the time of the inspection.

Rationale for Site Selection

Two CIs: Drs. Yasmin Karimi (Site #US02) and Catherine Thieblemont (Site #FR07), as well as the sponsor, Genmab US, Inc., were requested for clinical inspections in support of the application. The clinical sites were chosen primarily based on risk ranking in the BIMO clinical investigator site selection tool (CISST), numbers of enrolled subjects, and prior inspectional history, each of which may have an impact in the review division's clinical decision-making process.

Inspection Focus

The inspections were focused on subjects from the aNHL (i.e., LBCL) cohort of the Dose Expansion Part of the trial, in which the Sponsor seeks an indication.

III. RESULTS

1. Yasmin Karimi, M.D./Site: #US02
University of Michigan
1500 E Medical Center Dr, Spc 5911
Ann Arbor, MI 48109

Inspection Dates: 12/19/2022 – 12/22/2022

This was a comprehensive, PDUFA routine inspection of Dr. Karimi. This was her first FDA inspection.

At this site for Study GCT3013-01, 20 subjects were screened; 12 subjects were enrolled, which included the iNHL cohort, and 8 subjects were screen failures. At the time of the inspection, 3 subjects remained on treatment, 3 subjects discontinued enrollment due to disease progression, and 6 subjects were deceased.

During the inspection, subject records reviewed included informed consent, subject eligibility, concomitant medications, adverse events/serious adverse events, and protocol deviations. Informed consent was reviewed for all 12 enrolled subjects. Data verification was focused on the 9 subjects with aNHL. Seven out of 9 subject records with aNHL were reviewed for eligibility, adverse events/serious adverse events, protocol deviations, and primary efficacy endpoint. Source electronic medical records (EMRs) were compared with eCRFs and data line listings. The regulatory records reviewed included IRB submissions for initial approval and continuing reviews; protocol amendments; Form 1572s, financial disclosures, test article accountability, training records, and Curriculum Vitae (CVs) for the Principal Investigator (PI) and study team members.

The primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events. One subject was initially consented on an outdated ICD. The subject was later reconsented on the correct ICD. During the review of the pharmacy records, there were

examples of write-overs and documentation that appeared not to be contemporaneously written.

No Form FDA 483, Inspectional Observations, was issued at the conclusion of this inspection.

Reviewer's comment: the finding of the pharmacy records that appeared not to be contemporaneously written would not have significant impact on efficacy or safety results of the study. The finding that one subject was initially consented on an outdated ICD and reconsented on the correct ICD has no clinical significance.

2. Catherine Thieblemont, M.D./Site #FR07
Hospital Saint-Louis
1 Avenue Claude Vellefaux
Paris, 75475
France

Inspection Dates: 1/16/2023 – 1/20/2023

This was a comprehensive, PDUFA routine inspection of Dr. Catherine Thieblemont.

At this site for Study GCT3013-01, 9 subjects were enrolled in the aNHL cohort expansion part and consisted of subjects with diffuse large B-cell lymphoma. Four subjects were found to discontinue treatment: 2 subjects due to progressive disease (PD), and (2 subjects) from death due to PD.

Nine study subject records enrolled in the aNHL cohort were reviewed including informed consent, subject eligibility, protocol adherence, concomitant medications, and adverse events. For verification of the primary efficacy endpoint, records were reviewed to determine how images were obtained and submitted to the IRC for external independent review. Regulatory records reviewed included ethics committee oversight, IRB submissions, protocol amendments, test article accountability, and Form 1572s, in which Dr. Thieblemont signed the Investigator's GCP Agreement for Non-US Sites controlled document.

It was noted that the site did not maintain any type of log for medical history, concomitant medications and/or adverse events. The site did develop a document to capture adverse events which were noted during study visits. However, the form was not observed to have been used consistently throughout the trial. In general, adverse events observed within the subjects' record were consistent with the data listings except a few discrepancies, or potential discrepancies, noted in 4 subjects. For example, in 1 subject (Subject # (b) (6)), a physical exam included that the subject reported an ongoing fever but the corresponding summary notes from the subject's hospitalization did not report fever. The data listings did not report any adverse event for a fever for Subject # (b) (6) However, it did list that Subject # (b) (6) experienced an injection site reaction, but there were no corresponding documents within the Subject # (b) (6) record noting the reaction. Regarding potential discrepancies, 1 subject (Subject # (b) (6))

reported neutropenia a week apart but with no corresponding laboratory data that neutropenia had resolved in between events. One subject (Subject # (b) (6)) had a urine infection listed as an adverse event dated a week *after* bacteria was noted in urine lab report. One subject (Subject # (b) (6)) experienced an injection site reaction and Dr. Thieblemont annotated the document 2 years after the events. Lastly, the review of subject study records noted that intravenous (IV) contrast was not used for all radiographic scans associated with Subject # (b) (6) who experienced an allergy to the IV CT contrast while on the trial, and measurements for all of their target lesions were not assessed.

There were some issues with laboratory, EKG, and radiology reports. Some laboratory reports were missing, such as bilirubin and urinalysis. Detailed explanations were not recorded within the study visit regarding why the measurements were not taken. Regarding urinalysis specifically, there was 1 subject (Subject # (b) (6)) with 2 results: the site provided the query from the central laboratory stating the site should verify the result for specific gravity and send a corrected report. The site's interpretation was to send another document with the corrected result which resulted in the two documents. Print outs from the urine analyzer were not always maintained. For example, Subject # (b) (6) had an observed time on the urine strip changed (reflected the incorrect time) and the results were transcribed on the visit source document. In addition, the site failed to make immediate copies of the thermal paper print-out, therefore, several results were unreadable. Hand-written changes to the time were also noted with ECGs. Lastly, there were issues with finalized radiology reports: scans were read by multiple providers and the amended reports were challenging to identify in the medical records. However, the final report by a senior radiologist was ultimately included in the subject's hospital records. In addition, verification of the measurements reported within the data listings for this study required asking Dr. Kerviler, senior radiologist, to re-measure the organs during the inspection.

Reviewer's comment: The issues of ECG machine challenges, laboratory documentation and discrepancies, and final local radiology reports would not have significant impact on efficacy or safety results of the study.

Handwritten changes to time for ECGs would not have significant impact on efficacy or safety results of the study because this issue did not contribute to the primary efficacy endpoint. Furthermore, the site was already aware of this issue and had already requested 3 additional ECG machines to remediate this issue. Although the study records were not adequately organized, the site review was conducted using data from progress notes and source records, and data was eventually verified. Therefore, the documentation inconsistencies did not have a significant impact on the efficacy or safety results of the study. Because the issues with multiple urinalysis documentation and discrepancies did not contribute to the primary efficacy endpoint. Imaging records were sent to the IRC for review for the primary efficacy endpoint in accordance with trial protocol, therefore the local report of scans at this site would not have significant impact on efficacy or safety results of the study.

No Form FDA 483, Inspectional Observations, was issued at the conclusion of this inspection. In general, the inspection verified adequate source data for the inspected study subjects. The

primary efficacy endpoint data were verifiable.

3. Genmab U.S. Inc.
   777 Scudders Mill Rd.
   Bldg 2, 4th Floor
   Plainsboro, NJ 08536

   Inspection Dates: 1/9/2023 – 1/26/2023

   This inspection covered sponsor's study conduct related to Study GCT3013-01, concentrating on review of the aNHL arm of the expansion phase for efficacy and safety. The review focused on the clinical investigator sites chosen for inspection, Sites #US02 and #FR07, however, 6 sites monitoring files were reviewed during the inspection.

   Records reviewed during the inspection included:
   - Study documents (Parexel, now Calyx, provided the independent assessment of imaging studies and relevant clinical data)
   - Standard operating procedures (SOP)
   - Data collection and handling
   - Investigational product disposition
   - Safety reporting and handling
   - Selection of clinical investigators, sites, and monitors
   - Form FDA 1572s
   - Financial disclosures
   - Data monitoring committee activities

   Appropriate steps were taken by the sponsor to bring noncompliant sites into compliance. For example, Sites #FR04 and #UK03 were placed on recruitment hold following findings from a sponsor monitoring visit and internal audit, respectively. No sites were found to have inadequate monitoring. There was no under-reporting of serious adverse events (SAEs).

   The inspection found some minor issues: 1) inconsistent SUSAR dates and 2) clinicaltrials.gov language being out of date.

   Suspected unexpected serious adverse reaction (SUSAR) cases 2020-00503, 2020-00670, 2021-00146, 2021-00085, 2020-00502, and 2020-00673 were reviewed which showed that the report submission dates to the US FDA recorded in Genmab's Argus safety database did not match the date of the submission receipts in the safety database, as there were errors with a date conversion in the safety database. The Sponsor provided a presentation explaining the conversion discrepancy in the Argus safety database. The Sponsor reported that the firm was looking into the submission date conversion issue in this database.

   The master ICFs for Study GCT3013-01 versions 1.0 through 6.0 contained the statement, "A

description of this clinical trial is also available at http://www.ClinicalTrials.gov. The websites will not include information that can identify you" but not the full statement, "A description of this clinical trial is also available at http://www.ClinicalTrials.gov. The websites will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time," which was added to master ICF version 7.0 effective April 15, 2021.

Reviewer's comment: The issues with inconsistent SUSAR dates and clinicaltrials.gov language being out of date are unlikely to have significant impact on the safety or efficacy results of the study. The sponsor's corrective actions are acceptable.

Overall, the sponsor's oversight and monitoring for Study GCT3013-01 appear adequate. At the conclusion of the inspection, no Form FDA 483, Inspectional Observations, was issued.

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Leigh Marcus, M.D. Senior Physician
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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cc:

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Medical Officer/Nicole Sunseri

OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
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OSI/DCCE/GCPAB/Senior Physician/Leigh Marcus
OSI/GCPAB Program Analyst/Yolanda Patague

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 13, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761324
Product Name, Dosage Form, and Strength:	Epkinly (epcoritamab-xxxx)[a] Injection, 4 mg/0.8 mL, 48 mg/0.8 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Genmab US, Inc.
FDA Received Date:	September 21, 2022 and January 5, 2023
TTT ID #:	2022-1759
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

[a] The nonproprietary name for BLA 761324 has not been determined yet. The nonproprietary name epcoritamab-xxxx is used as a placeholder throughout this review.

1 REASON FOR REVIEW

As part of the approval process for Epkinly (epcoritamab-xxxx) Injection, we reviewed the proposed Epkinly Prescribing Information (PI), Medication Guide, container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Genmab US, Inc. submitted a 351(a) application to obtain marketing approval of Epkinly (epcoritamab-xxxx) Injection. Epkinly is proposed (b) (4)

We performed a risk assessment of the proposed container labels, carton labeling, PI, and Medication Guide for Epkinly Injection to determine whether there are significant concerns in terms of safety related to preventable medication errors. We note the proposed PI states: following administration of the first full dose, patients should (b) (4)

As such we reached out to the clinical team to determine how fast a reaction can occur once it starts and to obtain their thoughts on the statement in the PI. We defer to the clinical team for revisions to that part of the PI. Additionally, the proposed preparation instructions described in

the PI provides healthcare professionals with two different methods of dilution using either empty vials or syringes to prepare the 0.16 mg dose and 0.8 mg dose. We sent an Information Request (IR) for the detailed dose preparation instructions for the 0.16 mg dose and 0.8 mg dose that were used in the clinical study. The Applicant responded on January 5, 2023 with the detailed dose preparation instructions using empty vials only for the 0.16 mg dose and 0.8 mg dose.[b] As, such we have proposed additional revisions to the preparation instructions to require dilution of the product in vials only to be consistent with the clinical study and to prevent confusion from having multiple preparation instructions. See Appendix F for full information request.

We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. For the Division, we note the proprietary name is presented with the placeholder, "TRADENAME", the route of administration is abbreviated, and the use of symbols. In addition, we note lack of clarity in the recommended dosage, preparation instructions, administration instructions, dosage forms and strengths, and storage information. For the Applicant, we note the placeholders "TRADENAME" should be replaced with the conditionally acceptable proprietary, "EPKINLY" on the labels and labeling and the format of the expiration date is not defined. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container labels, carton labeling, PI, and Medication Guide that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Genmab US, Inc. to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Highlights and Full Prescribing Information

[b] Epkinly Injection 4 mg/0.8 mL, 48 mg/0.8 mL. BLA Number: BLA 761324, Sequence Number: 0013. DMEPA 2 INFORMATION REQUEST. Plainsboro (NJ): Genmab, Inc. 2023 JAN 05. Available from \\CDSESUB1\EVSPROD\bla761324\0013\m1\us\111-information-amendment\clinical-information-amendment.pdf and \\CDSESUB1\EVSPROD\bla761324\0013\m1\us\111-information-amendment\clinical-information-amendment-1.pdf

1. As currently presented, the proprietary name is denoted by the placeholder "TRADENAME". Replace all presentations of the placeholder "TRADENAME" with the conditionally acceptable proprietary name, EPKINLY.

B. Highlights of Prescribing Information
   1. Dosage and Administration
      a. Revise the first bullet using active voice to appear as, "For subcutaneous injection only."
      b. We recommend including a heading in the table for the recommended dosage for added clarity as follows:

Day of Treatment		Dose of Epkinly
Cycle 1	Day 1	0.16 mg
	Day 8	0.8 mg
	Day 15 and Day 22	48 mg
Cycles 2 and 3	Days 1, 8, 15, and 22	48 mg
Cycles 4 to 9	Days 1 and 15	48 mg
Cycles 10 and beyond	Day 1	48 mg

C. Prescribing Information
   1. Dosage and Administration Section
      a. The route of administration is abbreviated as "SC" and "IV". Presenting the route of administration as an abbreviation may lead to misinterpretation of the intended route of administration. We recommend revising "SC" to "subcutaneous" and "IV" to "intravenous".
      b. Section 2.1 Recommended Dosage
         i. The terms, [redacted] (b) (4) can be confusing to the intended users as the intermediate dose can be 0.8 mg and 0.16 mg under the missed or delayed dose section, which could lead to dosing errors. We recommend not using the terms, [redacted] (b) (4) [redacted] (b) (4) and refer to the doses per day of treatment.
         ii. As currently presented, Table 1 lacks clarity on the recommended dosage for Epkinly and is inconsistent with the Highlights of Prescribing Information. Therefore, we recommend revising Table 1 as follows:

Day of Treatment		Dose of Epkinly
Cycle 1	Day 1	0.16 mg
	Day 8	0.8 mg
	Day 15 and Day 22	48 mg
Cycles 2 and 3	Days 1, 8, 15, and 22	48 mg
Cycles 4 to 9	Days 1 and 15	48 mg
Cycles 10 and beyond	Day 1	48 mg

As currently presented, the missed or delayed dose schedule lacks clarity due to the layout in which the information is presented. Therefore, we recommend incorporating the text into a table for added clarity. We defer to the clinical team for the final action for missed or delayed dose schedule.

iii. We note the use of the symbol "-" used in Section 2.3 Dosage Modifications and Management of Adverse Reactions to represent the word "to". We recommend removing the use of the symbol and replacing it with its intended meaning of "to".

iv. As currently presented, Table 3: CRS Grading and Management Guidance contains the symbols, "≥", "≤", and ">". We recommend replacing the symbols, "≥", "≤", and ">" with the intended meanings.

v. We note in the Table 3: CRS Grading and Management Guidance that the temperature for fever is presented in Celsius only. We recommend including the temperature for fever to include Fahrenheit and Celsius [e.g. Fever greater than or equal to 100.4°F (38°C)].

vi. The unit of measure is missing in the dose ranges for pre-medications. We recommend revising the premedication dose ranges to include the unit of measure after each dose range [e.g. Acetaminophen (650 mg to 1,000 mg oral)].

c. Section 2.4 Preparation and Administration

i. The preparation instructions lack clarity, which may lead to product preparation errors. Therefore, we recommend the following revisions:

a. The administration of the 0.16 mg dose and 0.8 mg dose requires dilution prior to subcutaneous administration; however, this information is missing. We recommend adding the statement, "Read this entire section carefully before preparation of EPKINLY. Certain doses of EPKINLY require dilution prior to administration. Follow the preparation instructions provided below, as improper

preparation may lead to improper dose." to mitigate the risk of drug preparation errors.

b. Remove all instances of the terms, (b) (4), (b) (4) and refer to the doses per day of treatment.

c. We recommend revising the statement, (b) (4) to "The administration of EPKINLY takes place over the course of 28-day cycles, following the dosing schedule in Section 2.1." for clarity.

d. We recommend removing (b) (4)

e. Preparation of EPKINLY
Use aseptic technique to prepare EPKINLY.

Preparation instructions for 0.16 mg and 0.8 mg dose of EPKINLY

(b) (4)

(b) (4)

0.16 mg Dose Preparation Instructions
Use an appropriately sized, syringe and needle for each transfer step.

1. Prepare EPKINLY vial
   a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator.

(b) (4)

2. Perform first dilution
   a. (b) (4)
   b. Transfer 0.8 mL of EPKINLY into vial (b) (4)
   c. Transfer 4.2 mL of 0.9% Sodium Chloride Injection, USP into vial labeled as Dilution A. The initially diluted solution contains xx mg/mL of EPKINLY.
   d. Gently swirl the Dilution A vial for 30 to 45 seconds.

3. Perform second dilution
   a. (b) (4)
   b. Transfer 2 mL of solution from the (b) (4) The Dilution A vial is no longer needed.
   c. Transfer 8 mL of 0.9% Sodium Chloride Injection, USP into the Dilution B vial to make a final concentration of xx mg/mL.
   d. Gently swirl the Dilution B vial for 30 to 45 seconds.

4. Withdraw dose
   a. Withdraw 1 mL of the diluted EPKINLY from the Dilution B vial into a syringe.

5. Label syringe
   a. Label the syringe with the dose strength (0.16 mg) and the time of day.

Discard the (b) (4) vial (b) (4) (b) (4)

0.8 mg Dose Preparation Instructions

Use an appropriately sized, syringe and needle for each transfer step.

1. Prepare EPKINLY vial
   a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator.

(b) (4)

2. Perform dilution

(b) (4)

3. Withdraw dose

a. (b) (4)
4. Label syringe a. Label the (b) (4) syringe with the dose strength (0.8 mg) and the time of day.

Discard the (b) (4) vial (b) (4) (b) (4).

48 mg Dose Preparation Instructions

EPKINLY 48 mg/0.8 mL vial is supplied as ready-to-use solution that does not need dilution prior to administration.

1. Prepare TRADENAME vial a. Retrieve one 48 mg/0.8 mL EPKINLY vial from the refrigerator. b. Allow the vial to come to room temperature for xx minutes. c. Gently swirl the TRADENAME vial. DO NOT invert, vortex, or vigorously shake the vial.
2. Withdraw dose Withdraw 0.8 mL of EPKINLY into a syringe.
3. Label syringe a. Label the syringe with the dose strength (48 mg) and the time of day.

(b) (4)

Diluted EPKINLY Storage

Use diluted solution immediately. If not used immediately, store the solution refrigerated at 2°C to 8°C (36 F° to 46F°) for up to 24 hours or at room temperature 20°C to 25°C (68°F to 77°F) up to 12 hours from the start of dose preparation. The total storage time from the start of dose preparation to administration should not exceed 24 hours. Protect from direct sunlight. Allow EPKINLY solution to equilibrate to room temperature before administration. Discard unused EPKINLY solution beyond the allowable storage time.

Administration (b) (4)

Inject the required volume of EPKINLY into the subcutaneous tissue of the lower (b) (4) (b) (4) Change of injection site from the left or right side or vice versa is recommended, especially during the weekly administrations (Cycles 1 to 3).

D. Medication Guide

1. As currently presented, the proprietary name is denoted by the placeholder "TRADENAME". Replace all presentations of the placeholder "TRADENAME" with the conditionally acceptable proprietary name, EPKINLY.
2. How will I receive TRADENAME?

a. We recommend revising the first bullet statement to appear as, "You will receive EPKINLY by your healthcare provider as an injection under your skin (subcutaneous injection) in 28-day cycles, on a dosing schedule as follows:"

Cycle	**Dosing Schedule**
Cycles 1 to 3	Weekly
Cycles 4 to 9	Every other week
Cycles 10 and beyond	Every four weeks

3. What are the ingredients in TRADENAME?
   a. We recommend revising the active ingredient (b) (4) to include the nonproprietary name suffix place holder, "epcoritamab-xxxx".

4.2 RECOMMENDATIONS FOR GENMAB US, INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, the proprietary name is denoted by the placeholder "TRADENAME". Replace all presentations of the placeholder "TRADENAME" with the conditionally acceptable proprietary name, Epkinly.

2. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date.

B. Carton Labeling

1. The carton labeling does not contain instructions that this product must be administered by healthcare provider only. Failure to include instructions on the carton labeling may result in patients or caregivers administering the product, which may lead to medication errors. We recommend revising the statement for

the 4 mg/0.8 mL strength [redacted] (b) (4) to read "For subcutaneous injection after dilution by a healthcare provider only" to help alert patients and healthcare providers that the patient should take the product to their healthcare provider for administration. For the 48 mg/0.8 mL strength, we recommend revising the statement [redacted] (b) (4) to "For subcutaneous injection by a healthcare provider only."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Epkinly received on September 21, 2022 from Genmab US, Inc..

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Epkinly</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Nonproprietary Name</td><td>epcoritamab-xxxx</td></tr>
<tr><td>Indication</td><td>(b) (4)</td></tr>
<tr><td>Route of Administration</td><td>Subcutaneous</td></tr>
<tr><td>Dosage Form</td><td>Injection</td></tr>
<tr><td>Strength</td><td>4 mg/0.8 mL, 48 mg/0.8 mL</td></tr>
<tr><td>Dose and Frequency</td><td>(b) (4)</td></tr>
<tr><td>How Supplied</td><td>EPKINLY (epcoritamab-xxxx) injection is a sterile, clear to slightly opalescent, colorless to slightly yellow solution, (b) (4) free of visible particles, supplied in glass vials as follows:
<table>
<tr><th>Carton contents</th><th>NDC number</th></tr>
<tr><td>One 4 mg per 0.8 mL single-dose vial</td><td>NDC 82705-002-01</td></tr>
<tr><td>One 48 mg per 0.8 mL single-dose vial</td><td>NDC 82705-010-01</td></tr>
</table></td></tr>
<tr><td>Storage</td><td>Store (b) (4) refrigerated at 2°C to 8°C (36°F to 46°F). Keep in the original carton to protect from light. Do not freeze. Do not shake.</td></tr>
</table>

APPENDIX F. INFORMATION REQUEST

FDA Information Request: We note that the preparation instructions described in the Prescribing Information provides healthcare professionals with two different methods of dilution using either empty vials or syringes to prepare the 0.16 mg dose and 0.8 mg dose. We request that you provide the detailed dose preparation instructions for the 0.16 mg dose and 0.8 mg dose that were used in the clinical study to inform our review.

Applicant Response received on January 5, 2023: See \\CDSESUB1\EVSPROD\bla761324\0013\m1\us\111-information-amendment\clinical-information-amendment.pdf and \\CDSESUB1\EVSPROD\bla761324\0013\m1\us\111-information-amendment\clinical-information-amendment-1.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Epkinly labels and labeling submitted by Genmab US, Inc..

- Container label received on September 21, 2022
- Carton labeling received on September 21, 2022
- Prescribing Information and Medication Guide (Image not shown) received on September 21, 2022, available from \\CDSESUB1\EVSPROD\bla761324\0001\m1\us\114-labeling\draft\labeling\proposed.pdf

G.2 Label and Labeling Images

Container labels

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

NICOLE F IVERSON
02/13/2023 10:20:46 AM

HINA S MEHTA
02/14/2023 11:23:15 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: November 9, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead Cardiac Safety IRT, DCN

To: Natasha Kormanik
DHM2

Subject: QT Consult to BLA 761324 SDN 001

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 10/12/2022 regarding the sponsor's QTc assessment of epcoritamab. We reviewed the following materials:

- Sponsor's Modeling and Simulation Report (BLA761324/ SDN001)
- Previous IRT review for IND 135659 dated 8/7/2017 in DARRTS
- Sponsor's proposed label

1 Internal Comments for the Division

- A dedicated QTc assessment is not needed for monoclonal antibodies because there is not a biologic mechanism to directly hERG potassium channel (E14 Q&A 6.3).
- No formal QTc studies were conducted. Routine, safety ECGs and cardiac TEAEs do indicate that epcoritamab delays cardiac repolarization.

2 BACKGROUND

2.1 Product Information

The sponsor, Genmab US, Inc., is developing Epcoritamab (GEN3013, DuoBody®-CD3×CD20) for the treatment in adults of large B-cell lymphoma (LBCL) that has come back (relapsed) or did not respond to previous treatment (refractory) and who have received at least 2 prior therapies. As monotherapy it is for the treatment of diffuse large B-cell lymphoma (DLBCL) and as a combination drug it is with standard of care agents for DLBCL and follicular lymphoma (FL). It is a humanized bispecific antibody that induces T-cell-directed killing of CD20-positive cells by co-engaging CD3 on T cells and CD20-expressing B cells.

Dosage Form and Dosing: Epcoritamab will be administered as a subcutaneous (SC) injection in treatment cycles of 28 days. The epcoritamab drug product is provided in 2 concentrations: 5 mg/mL and 60 mg/mL. Each vial contains an extractable volume of 0.8 mL. Based on 0.8 ml volume, the 4 mg per 0.8 mL strength is a concentrate solution for injection which must be diluted prior to administration (priming and intermediate doses), whereas the 48 mg per 0.8 mL strength is a solution for injection (full dose). The dosing schedule is presented in Table 1

Table 1. Epcoritamab dosing schedule in different 28-days dosing cycles.

(b) (4)

Source: Proposed label

Pharmacokinetics: The pharmacokinetics of Epcoritamab is described in the proposed labeling provided by the sponsor. The Highlights of Clinical Pharmacology and Cardiac Safety have not yet been provided by the sponsor.

Following the recommended full SC dose of epcoritamab 48 mg, the geometric mean (% CV) Cmax of epcoritamab is 10.8 µg/mL (cv 41.7%) and Tmax occurs in 3 to 4 days in patients with LBCL. The metabolic pathway of epcoritamab has not been studied and the label mentions that like other protein therapeutics, epcoritamab is expected to be degraded into small peptides and amino acids via catabolic pathways. It is expected to undergo saturable target mediated clearance and the half-life is concentration dependent. With the full dose of 48 mg epcoritamab half-life ranges from 22 to 25 days based on the frequency of dosing.

No clinically important effects have been observed on the pharmacokinetics of epcoritamab based on age (20 to 89 years), sex, race/ethnicity (White, Asian, and Other), mild to moderate renal impairment and mild hepatic impairment. No patients with severe to end-stage renal disease (CLcr < 30 mL/min) or severe hepatic impairment have been studied. There is very limited data in moderate hepatic impairment, and therefore, the pharmacokinetics of epcoritamab are unknown in these populations.

Body weight (39 to 144 kg) is a significant factor on the pharmacokinetics of epcoritamab but it is not clinically relevant across body weight categories.

No formal drug interaction studies have been conducted. (b) (4)

2.2 Sponsor's Submission

Summary of Previous Communication:

In our previous review (dated 8/7/2017 in DARRTS –link above) it was conveyed to the sponsor that large, targeted proteins and monoclonal antibodies have a low likelihood of direct channel

interaction and therefore the sponsor's ECG monitoring schedule was reasonable for capturing any potential large indirect effects. Further in the Clinical Division's response in the pre-IND Written Responses (in DARRTS 8/14/2017) it was communicated that since GEN3013 is a monoclonal antibody, time-matched ECG monitoring with PK sampling was not necessary to evaluate the effect of GEN3013 on the QT/QTc interval but to consider including safety monitoring for cardiac adverse reactions as GEN3013 may be associated with cytokine release syndrome.

A dedicated QT trial was not conducted due to the inability to study epcoritamab in healthy subjects or expose subjects to supratherapeutic doses. In addition, as a bispecific antibody with MW ~149 kDa, epcoritamab is too large to directly inhibit the hERG channel and is therefore unlikely to directly impact cardiac repolarization.

Current Submission:

In the current submission (see population PK report), the sponsor assessed cardiac prolongation effect of epcoritamab in four scenarios:

i) Pooled data from dose escalation part of study GCT3013-01 and dose expansion part of study GCT3013-01 and GCT3013-04. In study GCT3013-01, single and triplicate ECGs were collected and centrally evaluated. A concentration-QTc analysis of the QTcF intervals was conducted using a linear mixed-effect modeling approach. A review of the QTcF data and the concentration-QTc relationship for epcoritamab revealed no significant association between epcoritamab concentrations and ΔQTcF.

   At the arithmetic mean predicted Cmax value of 11.7 µg/mL following the proposed QW dosing regimen, QTcF prolongation was predicted to be 0.76 msec, with the 95% CI upper bound of 3.40 msec.

ii) A similar concentration-QTc analysis was performed for the subjects from the dose escalation part only of study GCT3013-01.

iii) Concentration-QTc analysis was also performed for subjects with LBCL of dose escalation and expansion part of study GCT3013-01.

iv) Similar analysis was also performed for subjects with DLBCL of dose escalation part of study GCT3013-01.

Sampling:

In GCT3013-01, 12-lead ECGs including PR, QRS, QT, heart rate, and RR intervals were obtained for each subject during the trial at screening, Cycle 1 Days 1, 2, 4, 8, 9, 11, 15, and 22; Cycle 2 Days 1, 4, 8, 11, 15, and 22; Cycles 3 to 6 Days 1 and 15; and Cycle 7 Day 1 and beyond. ECGs were collected in triplicate in the Dose Escalation part and ECG data were read and interpreted centrally in the Dose Escalation part only. Any relationship between QTcF and PK concentrations across dose levels and time-points was investigated.

In GCT3013-04, 12-lead ECGs (in singlets) including PR, QRS, QT, heart rate, and RR intervals were obtained for each subject during the trial. In the Expansion part, ECG data were read and interpreted by a central cardiologist for the measurement of the cardiac intervals and morphologic assessment.

The concentration-QTc analysis population was defined as all subjects who had baseline QTc measurements and at least 1 matched pair of post dose QTc and concentration measurements. The relationship between epcoritamab plasma concentrations and change in QTcF from baseline (ΔQTcF) was investigated using a linear mixed-effect modeling approach with ΔQTcF as the dependent variable. The models were used to project the mean and 95% CIs of ΔQTcF at the mean values of observed Cmax following 48 mg doses. The predicted mean ΔQTcF values and the upper bound of the 95% CI were then compared with a 10 msec threshold.

The model had the following general equation:

$$\Delta QTcF = Intercept + \eta_{intercept} + (Slope + \eta_{slope}) \times C + Error$$

The Intercept is the population mean intercept representing ΔQTcF at zero concentration, Slope is the population mean slope describing the dependency of ΔQTc on concentration, C is the plasma concentration of epcoritamab, $\eta_{intercept}$ and η_{slope} are the random variables on the intercept and slope, and Error is the residual error term. Slope of the relationship was statistically significant if the p-value was below 0.05.

Results:

Parameters of ΔQTcF Models and Predicted ΔQTcF Change from Baseline are presented in Table 2. QTcF data and the concentration-QTc relationship for epcoritamab showed no effect of epcoritamab on ΔQTcF. For all four scenarios in the Table above with the mean predicted Cmax of 11.7 µg/mL following QW dosing regimen, the mean ΔQTcF prolongation ranged from -4.67 msec to 0.76 msec with the 95% CI upper bound ranging from 1.88 msec to 4.23 msec.

Table 2. Parameters of ΔQTcF Models and Predicted ΔQTcF Change from Baseline

Data set	Concentration-ΔQTcF relation			ΔQTcF for C_{max}=11.7 µg/mL	
	Slope	SE	P value	Estimate (msec)	One-sided upper 95% confidence bound (msec)
GCT3013-01 and GCT3013-04 (all histologies)	0.275	0.168	0.103	0.76	3.40
GCT3013-01 dose escalation (all histologies)	-0.349	0.487	0.478	-4.67	1.88
GCT3013-01 patients with LBCL	-0.0894	0.242	0.712	-0.06	4.23
GCT3013-01 patients with DLBCL	-0.0921	0.251	0.713	-0.21	3.84

Source: Modeling and simulation report, table 14, page 100.

In the aNHL pivotal expansion cohort from GCT3013-01, periodic ECG assessments were performed to capture potential ECG changes following treatment with epcoritamab.

- Postbaseline QTcF intervals >480 to 500 msec and >500 msec were reported in 4 (4.3%) subjects and 3 (3.2%) subjects, respectively, all in subjects with DLBCL. Of the 3 subjects with QTcF >500 msec, only 1 subject (Subject US02-2103) was reported with a TEAE of long QT syndrome, which was related to pre-existing condition requiring a pacemaker. The other 2 subjects had abnormalities that were not considered clinically meaningful and were not reported as AEs.
- 24 (15.3%) subjects with LBCL had a TEAE in the SOC of cardiac disorders, including 8 (5.1%) subjects with tachycardia and 5 (3.2%) subjects with sinus tachycardia; all other events had incidence <2%.
- Five (3.2%) subjects with LBCL had a TEAE in the SOC of cardiac disorders considered treatment related by the investigator, including 2 (1.3%) subjects with tachycardia, 2 (1.3%) subjects with sinus tachycardia, and 1 (0.6%) subject with sinus bradycardia.

The sponsor states that epcoritamab does not cause QT prolongation based on (i) the lack of a relationship between epcoritamab PK and ΔQTcF, (ii) the lack of a biologic mechanism for epcoritamab to directly impact QTcF, and (iii) the clinical safety findings that epcoritamab did not have a clinically relevant effect on cardiac repolarization or result in clinically meaningful cardiac AEs.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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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/

DEVI KOZELI on behalf of RAMAN K BAWEJA
11/09/2022 09:48:37 AM
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