CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761400Orig1s000

OTHER REVIEW(S)

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:	May 8, 2025
To:	Ashlee P. Bow, PharmD, AAHIVP Regulatory Project Manager **Division of Hematologic Malignancies II (DHM2)**
Through:	Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Valerie Guerrier, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	LYNOZYFIC (linvoseltamab-gcpt)
Dosage Form and Route:	injection, (b) (4)
Application Type/Number:	BLA 761400
Applicant:	Regeneron Pharmaceuticals, Inc.

1 INTRODUCTION

On January 10, 2025, in response to the Agency's Complete Response (CR) Letter dated August 20, 2024, Regeneron Pharmaceuticals, Inc. resubmitted for the Agency's review an original Biologics License Application (BLA) 761400 for LYNOZYFIC (linvoseltamab-gcpt) injection. With this submission, the Applicant proposes an indication for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4)

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 January 14, 2025 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for LYNOZYFIC (linvoseltamab-gcpt) injection.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Mitigation Assessment and Medication Errors Surveillance (DMAMES) and will be provided to DHM2 under separate cover.

2 MATERIAL REVIEWED

- Draft LYNOZYFIC (linvoseltamab-gcpt) injection MG received on January 10, 2025, and received by DMPP and OPDP on April 25, 2025.
- Draft LYNOZYFIC (linvoseltamab-gcpt) injection Prescribing Information (PI) received on January 10, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 25, 2025.
- Approved ELREXFIO (elranatamab-bcmm), COLUMVI (gloflitamab-gxbm), EPKINLY (epcoritamab-bysp), LUNSUMIO (mosunetuzumab-axgb), and TECVAYLI (teclistamab-cqyv) comparator labeling dated August 14, 2023, June 15, 2023, June 26, 2024, November 22, 2024, and May 28, 2024, respectively.

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
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

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/

RUTH I MAYROSH
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VALERIE GUERRIER
05/08/2025 12:53:50 PM

BARBARA A FULLER
05/08/2025 12:59:15 PM

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

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

Memorandum

Date: May 8, 2025

To: Ashlee Bow, Regulatory Project Manager,
Division of Hematologic Malignancies II (DHM2)

From: Valerie Guerrier, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for LYNOZYFIC™ (linvoseltamab-xxxx) injection, for intravenous use

BLA: 761400

Background:

In response to DHM2's consult request dated January 14, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original BLA submission for LYNOZYFIC™ (linvoseltamab-xxxx) injection, for intravenous use.

PI/Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 25, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide, and comments will be sent under separate cover.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on April 25, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Valerie Guerrier at (240) 402-2162 or Valerie.Guerrier@fda.hhs.gov.

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/s/

VALERIE GUERRIER
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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)

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

Date of This Review:	April 25, 2025
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761400
Product Name, Dosage Form, and Strength:	Lynozyfic (linvoseltamab-gcpt)[a] Injection, 5 mg/2.5 mL (2 mg/mL) and 200 mg/10 mL (20 mg/mL)
Applicant Name:	Regeneron Pharmaceuticals, Inc.
FDA Received Date:	March 17, 2025
TTT ID #:	2025-12581-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] The nonproprietary name, linvoseltamab-gcpt, was found conditionally acceptable on April 10, 2025.

1 PURPOSE OF MEMORANDUM

Regeneron Pharmaceuticals, Inc. submitted revised container labels and carton labeling received on March 17, 2025 for Lynozyfic. We reviewed the revised container labels and carton labeling for Lynozyfic (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,[b] which were communicated to the Applicant on March 11, 2025.[c]

2 CONCLUSION

In their response, the Applicant stated that the expiration date month format on the container labels and carton labeling is represented by numerical characters, which is consistent with FDA recommendations for expiration date formatting from a medication safety perspective. We have no further comments regarding expiration date format.

Additionally, the Applicant updated the container labels and carton labeling to include the non-proprietary name suffix "-gcpt" which was found conditionally acceptable on April 10, 2024.[d]

We have no additional recommendations at this time.

[b] Kundreskas, J. Label and Labeling Review for Lynozyfic (BLA 761400). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 APR 09. TTT ID: 2025-12581.
[c] Bow, A. FDA Communication: BLA 761400 linvoseltamab – Carton and Container comments – Response due March 18, 2025, 12:00 PM ET. Silver Spring (MD): FDA, CDER, DHM 2 (US); 2025 MAR 11. BLA 761400. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807a4467.
[d] Mena-Grillasca, C. Suffix Review for Nonproprietary Name for linvoseltamab. Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 APR 10. TTT ID: 2025-304.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON MARCH 17, 2025

Container Labels:

(b) (4)

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/s/

JODY K KUNDRESKAS
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NICOLE F IVERSON
04/25/2025 09:29:23 AM

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:	April 9, 2025
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761400
Product Name, Dosage Form, and Strength:	Lynozyfic (linvoseltamab-xxxx)[a] injection, 5 mg/2.5 mL (2 mg/mL) and 200 mg/10 mL (20 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Regeneron Pharmaceuticals, Inc.
FDA Received Date:	January 10, 2025, February 7, 2025, and February 11, 2025
TTT ID #:	2025-12581
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder linvoseltamab-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 INTRODUCTION

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

1.1 REGULATORY HISTORY

Regeneron Pharmaceuticals, Inc. previously submitted BLA 761400 on December 22, 2023. We completed a label and labeling review at that time.[b] Our recommendations were conveyed to the Applicant on May 22, 2024,[c] and the Applicant implemented all of our recommendations in their response, received June 3, 2024.[d] The Application received a Complete Response letter on August 20, 2024 due to issues with facility inspection deficiencies.[e]

Thus, Regeneron Pharmaceuticals, Inc. submitted a Class 2 Resubmission on January 10, 2025.[f]

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

The proposed Lynozyfic Prescribing Information (PI), Medication Guide (MG), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Hematologic Malignancies 2 (DHM 2) in Section 4 and for Regeneron Pharmaceuticals, Inc. in Section 5.

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[b] Kundreskas, J. Label and Labeling Review for Lynozyfic (BLA 761400). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAY 29. TTT ID: 2024-7649.

[c] Bow, A. FDA Communication: BLA 761400 linvoseltamab - FDA USPI Labeling Draft - Response due May 30, 2024, 3:00PM EST. Silver Spring (MD): FDA, CDER, DHM II (US); 2024 MAY 22. BLA 761400. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8076257e

[d] Prescribing Information for Lynozyfic (BLA 761400). Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2024 JUN 03. Available from: \\CDSESUB1\EVSPROD\bla761400\0038\m1\us\114-labeling\draft\annotated\annotated-uspi.docx.

[e] Wall, L on behalf of Mark Theoret, MD. Complete Response for BLA 761400. Silver Spring (MD): FDA, CDER, OND, Division of Hematologic Malignancies 2 (DHM 2) (US); 2024 AUG 20.

[f] Resubmission Following Complete Response Letter for linvoseltamab-gcpt (BLA 761400). Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2025 JAN 10. Available from: \\CDSESUB1\EVSPROD\bla761400\0051\m1\us\12-cover-letters\cover.pdf.

4 RECOMMENDATIONS FOR THE DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Prescribing Information

1. Section 2 Dosage and Administration

a. In Section 2.2, *Recommended Dosage*, the dose of Lynozyfic in Table 1 is currently presented under the column heading (b) (4) which may lead to confusion. We recommend ensuring that the description of the dose and the dose are presented under the column heading "LYNOZYFIC Dose".

b. In Section 2.3, *Pretreatment Medications*, the cross reference to Table 2 is missing in the preamble, which may lead to confusion. Revise "Administer the following pre-treatment medications before each dose of the LYNOZYFIC step-up dosing schedule, which includes step-up dose 1, step-up dose 2, and the first treatment dose, the second treatment dose, and if indicated, subsequent treatment doses (see Tables 1 and 3), to reduce the risk of CRS and/or IRR" to "Administer the following pre-treatment medications before each dose of the LYNOZYFIC step-up dosing schedule, which includes step-up dose 1, step-up dose 2, and the first treatment dose, the second treatment dose, and if indicated, subsequent treatment doses (see Tables 1, 2, and 3), to reduce the risk of CRS and/or IRR".

c. In Section 2.6, *Preparation and Administration*, the subheading Dilution is not properly prominent as it is not underlined like the other subheadings, which may cause it to be overlooked. We recommend underlining this subheading for increased prominence.

B. Medication Guide (MG)

1. As currently presented, the proprietary name is denoted by the placeholder "TRADENAME". We reference our April 8, 2025 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Lynozyfic, was found conditionally acceptable. We recommend replacing the placeholder "Trade name" with the conditionally acceptable proprietary name, Lynozyfic throughout the Medication Guide.

5 RECOMMENDATIONS FOR REGENERON PHARMACEUTICALS, INC.

A. General Comments (Container Labels and Carton Labeling)

1. As currently presented, MM, the format for the expiration date month is not defined. We are unable to assess the proposed expiration date month format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date month 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. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Lynozyfic received on February 7, 2025 from Regeneron Pharmaceuticals, Inc..

Table 2. Relevant Product Information for Lynozyfic	
Initial Approval Date	N/A
Nonproprietary Name	linvoseltamab-xxxx
Indication	for the treatment of adult patients (b) (4) [redacted] This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
Dosage Form	injection
Strength	5 mg/2.5 mL (2 mg/mL) and 200 mg/10 mL (20 mg/mL)
Route of Administration	Intravenous Infusion

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Lynozyfic</th></tr>
<tr><td>Dose and Frequency</td><td>
<table>
<tr><td>Dosing Schedule</td><td>Day</td><td colspan="2">Lynozyfic Dose</td></tr>
<tr><td rowspan="3">Step-up Dosing Schedule</td><td>Day 1</td><td>Step-up dose 1</td><td>5 mg</td></tr>
<tr><td>Day 8</td><td>Step-up dose 2</td><td>25 mg</td></tr>
<tr><td>Day 15</td><td>First treatment dose</td><td>200 mg</td></tr>
<tr><td>Weekly Dosing Schedule</td><td>One week after Day 15 treatment dose and once weekly from Week 4 to Week 13 for 10 treatment doses</td><td colspan="2">200 mg</td></tr>
<tr><td>Biweekly (Every 2 weeks) Dosing Schedule</td><td>Week 14 and every 2 weeks thereafter</td><td colspan="2">200 mg</td></tr>
<tr><td colspan="4">Patients who have achieved and maintained VGPR or better at or after Week 24 and received at least 17 doses of 200 mg</td></tr>
<tr><td>Every 4 weeks Dosing Schedule</td><td>At Week 24 or after and every 4 weeks thereafter</td><td colspan="2">200 mg</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>A clear to slightly opalescent, colorless to pale yellow solution in a single-dose vial. It is supplied as provided in Table 11.
Table 11: Packaging Configurations
<table>
<tr><th>Carton contents</th><th>NDC</th></tr>
<tr><td>One 5 mg/2.5 mL (2 mg/mL) single-dose vial</td><td>61755-054-01</td></tr>
<tr><td>One 200 mg/10 mL (20 mg/mL) single-dose vial</td><td>61755-056-01</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>Store unopened vial in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.</td></tr>
<tr><td>Container Closure</td><td>A 5 mL or 20 mL (b) (4) glass vial, a 20 mm elastomeric stopper, and a 20 mm aluminum seal cap with a flip-off button.</td></tr>
</table>

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Lynozyfic labels and labeling submitted by Regeneron Pharmaceuticals, Inc..

- Prescribing Information received on February 7, 2025, available from \\CDSESUB1\EVSPROD\bla761400\0055\m1\us\114-labeling\draft\labeling\proposed-uspi.pdf
- Medication Guide received on February 11, 2025, available from \\CDSESUB1\EVSPROD\bla761400\0056\m1\us\114-labeling\draft\labeling\med-guide.pdf
- Container labels received on January 10, 2025
- Carton labeling received on January 10, 2025

B.2 Container Labels and Carton Labeling Images

Container Labels:

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

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APPENDIX C. PREVIOUS DMEPA REVIEWS

On February 12, 2025, we searched for previous DMEPA reviews relevant to this current review using the terms, 'linvoseltamab' and '761400'. Our search identified 2 previous reviews[h,i] since the date of our last search on January 3, 2024, and we considered our previous recommendations to see if they are applicable for this current review.

[h] Kundreskas, J. Label and Labeling Review for Lynozyfic (BLA 761400). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 DEC 22. TTT ID No.: 2024-7649.

[i] Kundreskas, J. Review of Revised Label and Labeling for Lynozyfic (BLA 761400). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JUN 03. TTT ID No.: 2024-7649-1.

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/s/

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

REVIEW DEFERRAL MEMORANDUM

Date:	August 13, 2024
To:	Ashlee P. Bow, PharmD, AAHIVP Regulatory 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)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Patient Labeling Review Deferred: Medication Guide (MG)
Drug Name (established name):	LYNOZYFIC (linvoseltamab-gcpt)
Dosage Form and Route:	injection (b) (4)
Application Type/Number:	BLA 761400
Applicant:	Regeneron Pharmaceuticals, Inc.

1 INTRODUCTION

On December 22, 2023, Regeneron Pharmaceuticals, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761400 for LYNOZYFIC (linvoseltamab-gcpt) injection. With this submission, the Applicant proposes an indication for the treatment of adult patients with relapsed or refractory multiple myeloma [redacted] (b) (4)

On January 3, 2024, the Division of Hematologic Malignancies II (DHM2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for LYNOZYFIC (linvoseltamab-gcpt) injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed MG for LYNOZYFIC (linvoseltamab-gcpt) injection.

2 CONCLUSIONS

Due to facility inspection deficiencies, DHM2 plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the CR letter. Please send us a new consult request at such time.

Please notify us if you have any questions

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/s/

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

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

Memorandum

Date: July 18, 2024

To: Ashlee Bow, Regulatory Project Manager,
Division of Hematologic Malignancies II (DHM2)

From: Valerie Guerrier, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for LYNOZYFIC™ (linvoseltamab) injection, for intravenous use

BLA: 761400

This memo is in response to DHM2's labeling consult request dated January 3, 2024. OPDP defers comment on the proposed labeling at this time and requests that DHM2 submit a new consult request during the subsequent review cycle. If you have any questions, please contact Valerie Guerrier at (240) 402-2162 or Valerie.Guerrier@fda.hhs.gov.

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/s/

VALERIE GUERRIER
07/18/2024 08:40:43 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)

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Date of This Review:	June 14, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761400
Product Name, Dosage Form, and Strength:	Lynozyfic (linvoseltamab-(b) (4)) Injection, 5 mg/2.5 mL (2 mg/mL) and 200 mg/10 mL (20 mg/mL)
Applicant Name:	Regeneron Pharmaceuticals, Inc.
FDA Received Date:	June 3, 2024
TTT ID #:	2024-7649-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] The nonproprietary name "linvoseltamab-(b) (4)" was found conditionally acceptable for this BLA on June 5, 2024.

1 PURPOSE OF MEMORANDUM

Regeneron Pharmaceuticals, Inc. submitted revised container labels and carton labeling received on June 3, 2024 for Lynozyfic. We reviewed the revised container labels and carton labeling for Lynozyfic (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.[b]

2 CONCLUSION

Regeneron Pharmaceuticals, Inc. implemented all of our recommendations. However, we note that the proposed nonproprietary name suffix, (b) (4) was found conditionally acceptable on June 5, 2024 and the labels and labeling should be revised to include the suffix.

3 RECOMMENDATIONS FOR REGENERON PHARMACEUTICALS, INC.

A. General Comments (Container Labels & Carton Labeling)

1. As currently presented, the nonproprietary name suffix is designated as -xxxx. Please refer to the General Advice Letter issued on June 12, 2024 which notified you of the nonproprietary name suffix found conditionally acceptable for your proposed product. Should your BLA be approved during this review cycle, linvoseltamab-(b) (4) will be the proper name designated in the license. Revise the nonproprietary name on all the labels and labeling to incorporate the FDA-designated nonproprietary name suffix, (b) (4), appended to the core name, linvoseltamab so that the proper name appears as linvoseltamab-(b) (4) throughout the labels and labeling.

[b] Kundreskas, J. Label and Labeling Review for Lynozyfic (BLA 761400). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAY 29. TTT ID: 2024-7649.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JUNE 3, 2024

Container Labels:

(b) (4)

Carton Labeling:

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JODY K KUNDRESKAS
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NICOLE F IVERSON
06/14/2024 04:19:00 PM

CLINICAL INSPECTION SUMMARY

Date	6/11/2024
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	Ashlee Bow, Regulatory Project Manager Deepti Telaraja, M.D., Clinical Reviewer Bindu Kanapuru, M.D., Team Leader Nicole Gormley, M.D. Division Director Division of Hematologic Malignancies 2 (DMH2) Office of Oncologic Diseases (OOD)
sNDA/BLA #	BLA 761400
Applicant	Regeneron Pharmaceuticals, Inc.
Drug	Linvoseltamab (REGN5458)
NME	Yes
Review Priority	Priority
Proposed Indication	Treatment of adult patients with relapsed or refractory multiple myeloma (b) (4)
Consultation Request Date	2/23/2024
Summary Goal Date	6/15/2024
Action Goal Date	8/19/2024
PDUFA Date	8/22/2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study R5458-ONC-1826 were submitted to the Agency in support of this Biologics License Application (BLA) for linvoseltamab for treatment of adult patients with relapsed or refractory multiple myeloma (b) (4)

Three domestic clinical investigators (CI), Drs. Naresh Bumma (Site #840009), Hans Lee (Site # 840011), and Attaya Suvannasankha (Site #840012), as well as the Sponsor, Regeneron Pharmaceuticals, Inc. (Regeneron), were inspected for Study R5458-ONC-1826.

Based on the inspections of three CIs and the Sponsor, no significant regulatory violations were identified. The clinical data generated by these CI sites are verifiable. Study R5458-ONC-1826 appears to have been conducted adequately, and the data generated by these sites and reported by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Linvoseltamab is a human IgG4-based bispecific antibody that binds to CD3, a T-cell antigen associated with the T-cell receptor complex, and BCMA, which is expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. Simultaneous engagement of both arms of linvoseltamab results in formation of a synapse between the T cell and the tumor cell, resulting in T cell activation and generation of polyclonal cytotoxic T-cell response, which result in redirected lysis of the targeted cells, including malignant multiple myeloma B-lineage cells. Linvoseltamab is being investigated as a treatment of subjects with relapsed or refractory multiple myeloma (RRMM). The sponsor submitted the results of Study R5458-ONC-1826, an open-label, multicenter, dose-escalation, dose-expansion, study of linvoseltamab administered as an IV infusion in adult subjects with RRMM, to support efficacy and safety for the proposed indication.

Study R5458-ONC-1826

Title: "Phase 1/2 FIH Study of REGN5458 (anti-BCMA × anti-CD3 Bispecific Antibody) in Patients with Relapsed or Refractory Multiple Myeloma"

Study R5458-ONC-1826 was an open-label, multicenter, dose-escalation, dose-expansion, study of linvoseltamab administered as an IV infusion in adult subjects with RRMM. The study consisted of 2 phases. Phase 1 was designed to explore the safety and tolerability of escalating dose levels: 9 DLs ranging from 3 to 800 mg of linvoseltamab. The Phase 1 portion of the study followed a modified 3+3 dose escalation design with a 28-day dose-limiting toxicity (DLT) observation period to assess the safety of linvoseltamab and to select 1 or more recommended Phase 2 dose regimens (RP2Ds) of linvoseltamab IV as monotherapy. The Phase 2 portion of the study consisted of 2 cohorts designed to evaluate the safety and efficacy of 2 full doses of linvoseltamab:

- Cohort 1: 5 mg initial dose at week 1, 25 mg intermediate dose at week 2, and 50 mg full dose at week 3
- Cohort 2: 5 mg initial dose at week 1, 25 mg intermediate dose at week 2, and 200 mg, full dose at week 3 and thereafter

The study duration was up to approximately 24 months, including a screening period (up to 28 days), a treatment period (40 weeks), and a core follow-up period (approximately 24 weeks) followed by an extended follow-up period of approximately 36 weeks for the determination of durable clinical activity and safety (approximately 60 weeks total follow-up period). Treatment was until disease progression, intolerable AEs, withdrawal of consent, or study withdrawal criterion met.

In Phase 1, subjects must have had disease progression on or after 3 prior lines of therapy or who are triple-refractory, or progression on or after an anti-CD38 antibody and have disease that is "double refractory" to a PI and an IMiD, or intolerance of therapy. In Phase 2, patients (through Protocol Amendment 5) were required to be triple-refractory and penta-exposed. Triple-refractory was defined as being refractory to prior treatment with at least 1 anti-CD38 antibody, a PI, and an IMiD. Penta-exposed was defined as having prior exposure to 2 PIs, 2 IMiDs (lenalidomide and pomalidomide), and 1 anti-CD38 mAb. Beginning in Protocol Amendment 6, Phase 2 inclusion required patients to have experienced disease progression on or after at least 3 lines of therapy (including a PI, an IMiD, and an anti-CD38 antibody) or disease must be triple refractory, defined as being refractory to prior treatment with at least 1 PI, 1 IMiD, and an anti-CD38 antibody.

The primary objectives of Study R5458-ONC-1826 were:

Phase 1:

- To assess the safety, tolerability, and DLTs of linvoseltamab administered IV
- To determine the maximum tolerated dose (MTD) as R2PD of linvoseltamab

Phase 2:

- To study the antitumor activity of linvoseltamab by overall response rate (ORR) in subjects with RRMM as assessed by independent central review committee (IRC)

Efficacy was established based on ORR as assessed by an IRC using International Myeloma Working Group (IMWG) Criteria. The analyses of ORR were performed when all patients either completed at least 32 weeks of response assessment or discontinued efficacy evaluations early. The safety analysis sets included either any subject who received any dose of linvoseltamab or who received 1 dose at any dose level. The main safety endpoint of concern was cytokine-release syndrome (CRS), consistent with the mechanism of action of linvoseltamab.

The trial was conducted in 23 centers in 6 countries. The study enrolled 117 subjects treated at the registrational dose 200mg of linvoseltamab across both Phase 1 and 2 and were included as the primary efficacy population in the submission. Subjects first enrolled to Study R5458-ONC-1826 on January 23, 2019. Data cut-off date for the primary analysis was September 8, 2023. The study was ongoing at the time of the inspection.

III. RESULTS

1. Naresh Bumma, M.D./Site # 840009
   241 W 11th Ave
   Columbus, OH 43201-2356
   Inspection Dates: 4/29/2024 – 5/3/2024

   This was a comprehensive, PDUFA routine inspection of Dr. Naresh Bumma. This was his first FDA inspection.

   At this site for Study R5458-ONC-1826, 54 subjects were screened: 6 subjects were screen failures, and 48 subjects were enrolled into either Phase 1 or Phase 2; 19 subjects were enrolled into the proposed population who were treated at the registrational dose. Two subjects discontinued to due to adverse events (AEs): Subject # (b) (6) due to pneumocystis jirovecii pneumonia and progressive disease; Subject # (b) (6) from pseudomonal sepsis; 2 subjects withdrew due to physician decision; 5 subjects were currently receiving treatment; 10 subjects due to progressive disease.

   During the inspection, subject records reviewed included Informed Consent documents (ICDs), subject case history records, eligibility criteria, protocol deviations, adverse event reporting, and the majority of concomitant medications. The regulatory documents reviewed Institutional Review Board (IRB) submissions, protocol amendments, financial disclosures, 1572s, investigational product (IP) accountability records, and training.

   The primary efficacy endpoint data were verifiable. The inspection noted several underreporting non-serious AEs in three subjects: Subject # (b) (6) Grade 1 Cytokine Release Syndrome (CRS), Grade 2 Neurotoxicity (subsequently changed to "Confusion" from the etiology of fever), and Grade 1 Urinary Incontinence; Subject # (b) (6) Grade 1 agitation; and Subject # (b) (6) urinary incontinence. There were no underreported serious adverse events (SAEs).

   Reviewer's comment: The above underreported AEs were considered as low-grade AEs and have been included in the proposed labeling. Because the study is still active, the site added those underreported AEs to the CRF during the inspection. Although these AEs should have been reported timely, it appears no significant impact on the safety profile of the product.

   The inspection verified adequate source data for the study subjects at this site.

2. Hans Lee, M.D./Site # 840011
   1515 Holcombe Blvd.
   Houston, Texas 77030

   Inspection Dates: 4/15/2024 – 4/19/2024

This was a comprehensive, PDUFA routine inspection of Dr. Hans Lee. The previous FDA inspection was conducted on 1/10/2020 which noted not conducting an investigation in accordance with the investigational plan, specific to improper dosing of the study drug.

At this site for Study R5458-ONC-1826, 19 subjects were screened and consented: 12 subjects were enrolled in the proposed population who were treated at the registrational dose. Four subjects were still on treatment while 8 subjects were discontinued: 1 subject due to death, 4 subjects due to disease progression, and 3 subjects withdrew consent.

During the inspection, subject records reviewed included informed consent documents (ICDs), subject case history records, eligibility criteria, disposition, the efficacy endpoint, protocol deviations, and adverse event reporting. The regulatory documents reviewed Institutional Review Board (IRB) documents, protocol amendments, financial disclosures and 1572s, IP accountability records, and training.

The primary efficacy endpoint data were verifiable. There were no underreported AEs, or SAEs.

The inspection verified adequate source data for all of the study subjects. Overall, Study R5458-ONC-1826 appears to have been conducted adequately at this site.

3. Attaya Suvannasankha, M.D./Site: # 840012
   535 Barnill Drive
   Indianapolis, Indiana 46202

   Inspection Dates: 4/22/2024 –4/24/2024

   This was a comprehensive, PDUFA routine inspection of Dr. Attaya Suvannasankha. The previous FDA inspection in 5/2021 was virtual due to COVID-19 restrictions and did not identify significant regulatory violations.

   At this site for Study R5458-ONC-1826, 22 subjects were screened and 11 subjects were enrolled. One subject completed the treatment phase of the study, 4 subjects discontinued due to death (Covid-19 or non-drug related), 2 subjects due to noncompliance, 1 subject withdrew consent, and 1 subject (Subject # (b) (6)) due to AE of encephalopathy (including SAE of immune effector cell-associated neurotoxicity syndrome [ICANS] and proceeded by CRS and urinary tract infection).

   During the inspection, 11 subject records were reviewed which included ICDs, subject case history records, eligibility criteria, protocol deviations, and adverse event reporting. The regulatory documents reviewed IRB submissions for initial approval and continuing reviews, protocol amendments, financial disclosures, investigational product (IP) accountability records, and training.

The primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of serious adverse events (SAEs), nor AEs.

The inspection verified adequate source data for the study subjects. Overall, Study R5458-ONC-1826 appears to have been conducted adequately at this site.

4. Regeneron Pharmaceuticals, Inc.
   777 Old Saw Mill River Road
   Tarrytown, NY 10591-6707

   Inspection Dates: 4/15/2024 – 5/1/2024

   This inspection covered the Sponsor's study conduct related to Study R5458-ONC-1826. The previous inspection of Regeneron during 1/8-19/2024 did not identify significant regulatory violations.

   Records reviewed during the inspection included:

   - Standard operating procedures (SOP)
   - Monitoring plan, procedures, and activities
   - Data collection and handling
   - Independent review committee (IRC) charter (Calyx) and study documents
   - Primary efficacy data, including IRC assessment of tumor imaging
   - Electronic records and record retention
   - IP accountability
   - Safety reporting and handling including reporting of SAEs, i.e., deaths (Argus)
   - Selection of clinical investigators, sites, and monitors
   - Form FDA 1572s for CIs in the U.S.; GCP agreements for foreign CIs
   - Financial disclosures
   - Contracts

   Regeneron had agreement with CRO (b) (4) to assist in site selection and CI recruitment, as well as monitoring from site initiation to closeout. Four sites: Site #840006, Site #840010, Site #840011, Site #840012 were reviewed for monitoring reports and other documents during this inspection. Two sites, Site #840006 (Dr. Hoffman – Miami) and Site # 840010 (Dr. Dhodapkar – Atlanta) had enrollment holds based on data backlog issues in 2021 attributed to COVID-19. For Site 840006, Dr. James Hoffman was placed on hold from September 9, 2021, through February 11, 2022, due to backlog of data entry, query response, consenting issues, site training issues, lack of documentation and communication with the clinical research associate (CRA). Regeneron and (b) (4) identified these were associated with a PI change and staff resourcing issues due to the COVID-19 pandemic and a corrective action plan was created. Likewise for Site 840010, Dr. Dhodapkar was placed on enrollment hold from June 16, 2021, through January 26,

2022, due to a backlog

of data entry and query responses. Regeneron and (b) (4) identified the site experienced a staff resourcing issue due to the COVID-19 pandemic. No sites which were terminated for serious GCP non-compliance.

The primary efficacy endpoint ORR by IRC for Site #840006, Site #840010, Site #840011, Site #840012 was verified from the data listings provided.

Overall, the sponsor's oversight and monitoring for Study R5458-ONC-1826 appears to have been conducted adequately.

{See appended electronic signature page}

Leigh Marcus, M.D. Senior Physician
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Division of Hematologic Malignancies 2 (DMH2)

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/s/

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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:	May 29, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761400
Product Name, Dosage Form, and Strength:	Lynozyfic (linvoseltamab-xxxx[a]) Injection, 5 mg/2.5 mL (2 mg/mL) and 200 mg/10 mL (20 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Regeneron Pharmaceuticals, Inc
FDA Received Date:	December 22, 2023
TTT ID #:	2024-7649
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] The proposed nonproprietary name and the suffix for this BLA has not yet been determined, the nonproprietary name placeholder, linvoseltamab-xxxx, is used throughout this review to refer to the nonproprietary name and suffix for this product.

1 REASON FOR REVIEW

As part of the approval process for Lynozyfic (linvoseltamab-xxxx) Injection, we reviewed the proposed Lynozyfic Prescribing Information (PI), Medication Guide (MG), 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
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

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 CONCLUSION

The proposed Lynozyfic Prescribing Information (PI), Medication Guide (MG), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Hematologic Malignancies 2 (DHM 2) in Section 4 and for Regeneron Pharmaceuticals, Inc in Section 5.

4. RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Prescribing Information

1. General Comments

a. As currently presented, the proprietary name is denoted by the placeholder "TRADENAME". We reference our March 21, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Lynozyfic, was found conditionally acceptable. We recommend replacing the placeholder "TRADENAME" with the

conditionally acceptable proprietary name, Lynozyfic throughout the Prescribing Information.

2. Highlights of Prescribing Information

   a. The recommended dosage table does not match Table 1: Recommended Dosage in section 2. Providing inconsistent dosing instructions may result in misinterpretation of the recommended dosing. We recommend revising this table to match Table 1 (see below recommendation). The [redacted] (b) (4) is not needed in the Highlights of Prescribing Information, and may be left off for conciseness.

3. Section 2 Dosage and Administration Section

   a. General Comments

      i. The [redacted] (b) (4) is not required to be included [redacted] (b) (4) throughout section 2. We recommend removing [redacted] (b) (4) [redacted] (b) (4) throughout section 2 to reduce clutter.

      ii. The route of administration is abbreviated as IV throughout the Dosage and Administration Section. Presenting the route of administration as an abbreviation may lead to misinterpretation of the correct route of administration. We recommend revising "IV" to "intravenous" or "intravenously".

   b. As currently presented in section 2.2, *Recommended Dosage*, Table 1 lacks readability and clarity on the recommended dosage for Lynozyfic. Failure to provide clear dosing instructions may lead to medication errors. We recommend revising Table 1 as follows:

Dosing Schedule	Day	TRADENAME Dose		Duration of Infusion
Step-up Dosing Schedule	Day 1	Step-up dose 1	5 mg	4 hours
	Day 8	Step-up dose 2	25 mg	
	Day 15	First treatment dose	200 mg	
Weekly Dosing Schedule	One week after Day 15 treatment dose and once weekly from Week 4 to Week 13 for 10	Second and subsequent treatment doses	200 mg	1 hour for the second treatment dose and 30 minutes for subsequent doses[1]

Dosing Schedule	Day	TRADENAME Dose		Duration of Infusion
	treatment doses			
Biweekly (Every 2 Weeks) Dosing Schedule	Week 14 and every 2 weeks thereafter	Subsequent treatment doses	200 mg	30 minutes
Patients who have achieved and maintained VGPR or better and received at least 17 doses of 200 mg at Week 24				
Every 4 Weeks Dosing Schedule	Week 24 and every 4 weeks thereafter		200 mg	30 minutes
[1]For patients who experienced CRS with the previous dose of LYNOZYFIC, the duration of infusion should be maintained at the duration of the previous infusion; reduce the duration of infusion sequentially in subsequent doses in patients who do not experience CRS (e.g., 4 hours, 1 hour, then 30 minutes).				

c. The heading of Section 2.3, [redacted] (b) (4) is inconsistent with the content within that section. Providing unclear headings may result in confusion. Revise this heading to *Pretreatment Medications*. Additionally,

    i. The unit of measure (e.g., mg) is missing in the dose ranges for premedications and some doses are presented as a large number without a comma. This may lead to confusion and potential risk of wrong dose error. Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000". We recommend revising the premedication dose ranges to include the unit of measure after each dose range and large numbers to have a comma (e.g., 650 mg to 1,000 mg oral).

d. As currently presented, Table 3 in section 2.4, *Restarting TRADENAME after Dosage Delay*, contains the symbols "≤" and ">". Error prone symbols may lead to misinterpretation and medication error. We recommend replacing the symbols with their intended meanings.

e. In section 2.5, *Management of Adverse Reactions*, Table 4, Table 5, and Table 6 can be adjusted to improve the readability and clarity of information presented.

    i. As currently presented, Table 4, Table 5, and Table 6 contain the symbols "≤" and ">" regarding days since last dose. Error prone

symbols may lead to misinterpretation and medication error. We recommend replacing these symbols with their intended meanings.

ii. Laboratory values are presented with a trailing zero throughout Table 6, which can lead to tenfold misinterpretations when the decimal point is overlooked (e.g., 1.0 x 10^9/L is read as 10 x 10^9/L). Revise this laboratory value to remove the trailing zeros (e.g., 1 x 10^9/L).

f. The preparation instructions in section 2.6, *Preparation and Administration*, lack clarity, which may lead to product preparation errors. Therefore, we recommend the following revisions:
   i. Bullet the instructions for improved readability.
   ii. Remove "Discard any unused portion left in the vial." as this information will be relocated to the dilution instructions.
   iii. Revise the second paragraph under Preparation to standard language: "Parenteral drug products could be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.".
   iv. Add a bullet in the third position that states "Determine the dose, total volume of TRADENAME solution, and the number of TRADENAME vials needed (see Table (b) (4)).".
   v. Add a Dilution subheading underneath the third bullet.
   vi. Revise the dilution instructions into two bullets as follows:
      - Withdraw the desired dose from the vial of TRADENAME and transfer into an infusion bag [polyvinyl chloride (PVC) or polyolefin (PO)] of 0.9% Sodium Chloride Injection, according to Error! Reference source not found.. Discard any unused portion left in the vial.
      - Mix diluted solution by gentle inversion. Do not shake the solution.
   vii. Table (b) (4) should be revised for clarity, to reduce clutter, and to ensure that the unit of measure follows each numerical expression of dose, concentration, or volume. Revise to:

Table (b) (4) Dilution of TRADENAME.

TRADENAME dose	TRADENAME Vial Strength	Volume of TRADENAME to be Added to the Infusion Bag	Size of 0.9% Sodium Chloride Injection Infusion Bag (PVC or PO)
2.5 mg[a]	5 mg/2.5 mL	1.25 mL	50 mL
5 mg	5 mg/2.5 mL	2.5 mL	50 mL or 100 mL
25 mg	5 mg/2.5 mL	12.5 mL	50 mL or 100 mL
200 mg	200 mg/10 mL	10 mL	50 mL or 100 mL

[a] Modified dose due to adverse event. For instructions on when to use the modified dose refer to Table (b) (4)

g. The storage condition heading for the prepared infusion solution is unclear and important information may be overlooked. Including clear information on post-dilution storage will inform healthcare providers during product preparation and minimize the risk of administering deteriorated products. We recommend revising the section heading (b) (4) to "Diluted TRADENAME Storage".
    i. Revise (b) (4) to "Use diluted TRADENAME immediately. If not used immediately, store the solution:"

4. Section 16 How Supplied/Storage and Handling Section
    a. As currently presented, the term "dose" to describe the available product is confusing as the information listed refers to the product strength and not all of the doses. Using confusing terminology may lead to medication errors. We recommend revising (b) (4) to "It is supplied as provided in Table (b) (4)".
        i. We also recommend revising the title of Table (b) (4) to "Package Configurations".
        ii. Additionally, we recommend revising the leftmost column of Table (b) (4) TRADENAME Dosage Strengths from (b) (4) (b) (4) to "Carton Contents" and additionally providing the concentration in parenthesis and "single-dose vial" next to each strength.
    b. The (b) (4) is listed. Medication selection errors may occur (b) (4) We recommend removing (b) (4) in Table (b) (4) TRADENAME Dosage Strengths.

B. Medication Guide
    1. As currently presented, the proprietary name is denoted by the placeholder "Trade name". We reference our March 21, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Lynozyfic, was found conditionally acceptable. We recommend replacing the placeholder "Trade name" with the conditionally acceptable proprietary name, Lynozyfic throughout the Medication Guide.

5. RECOMMENDATIONS FOR REGENERON PHARMACEUTICALS, INC

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

A. General Comments (Container labels & Carton Labeling)

1. The 200 mg/10 mL (20 mg/mL) strength is not clearly differentiated [redacted] We recommend revising [redacted] the 200 mg/10 mL strength [redacted]

B. Carton Labeling

1. The [redacted] proprietary name [redacted] which may lead to misinterpretation of the proprietary name. [redacted] Delete, move, and/or [redacted] the proprietary name.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lynozyfic received on December 22, 2023 from Regeneron Pharmaceuticals, Inc.

Table 2. Relevant Product Information for Lynozyfic	
Initial Approval Date	N/A
Nonproprietary Name	linvoseltamab-xxxx
Indication	For the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4)
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	5 mg/2.5 mL (2 mg/mL) and 200 mg/10 mL (20 mg/mL)
Dose and Frequency	(b) (4)

Table 2. Relevant Product Information for Lynozyfic	
How Supplied	TRADENAME (linvoseltamab-xxxx) injection is a clear to slightly opalescent, colorless to pale yellow solution (b) (4) (b) (4)
Storage	Store unopened vial in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.
Container Closure	The primary container closure system consists of a 5 mL or 20 mL (b) (4) clear glass vial, a 20 mm elastomeric stopper, and a 20 mm aluminum seal cap with a flip-off button.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 3, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, '761400', 'Lynozyfic', and 'linvoseltamab'. Our search identified no previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Lynozyfic labels and labeling submitted by Regeneron Pharmaceuticals, Inc.

- Container label received on December 22, 2023
- Carton labeling received on December 22, 2023
- Prescribing Information (Image not shown) received on December 22, 2023, available from \\CDSESUB1\EVSPROD\bla761400\0001\m1\us\114-labeling\draft\labeling\proposed-uspi.pdf
- Medication Guide received on December 22, 2023, available from \\CDSESUB1\EVSPROD\bla761400\0001\m1\us\114-labeling\draft\labeling\med-guide.pdf

F.2 Label and Labeling Images

Container labels:

[b] 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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Clinical Review Memorandum

Division of Hepatology and Nutrition
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

BLA	761400
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Linvoseltamab
Indication	Multiple Myeloma
Applicant	Regenergon Pharmaceuticals, Inc
Requesting Division	Division of Hematological Malignancy
Primary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Signatory Authority	Joseph Toerner, MD, MPH Director, OPE/OSE
Assessment Date	May 9, 2024

I. Executive Summary

The Sponsor identified five subjects meeting liver analyte criteria for Hy's Law. The Division of Hematologic Malignancy (DHM) requested the Division of Hepatology and Nutrition (DHN) DILI Team assess these five cases for attribution to linvoseltamab (LNV). DHM did not request further assessments for DILI risk. None of the five cases of concern were attributable to DILI. All five had clear and compelling non-DILI explanations for the liver analyte elevations or liver injury. Based on this focused review, we do not see any hold issues or actionable items in terms of DILI risk.

II. Background

Linvoseltamab (LNV) is a human IgG-4 bispecific, monoclonal antibody that binds the T-cell CD3 antigen and B cell maturation antigen (BCMA). BCMA is on the surface of malignant multiple myeloma (MM) cells. Therefore, LVN creates a bridge between an immune effector T-cell and targeted malignant B-cell. The closeness of the two cells is expected to lead to "T-cell activation and…polyclonal cytotoxic T-cell response, which result in redirected lysis of the

targeted cells."[1] The Sponsor suggests this effect does not require major histocompatibility complex (HMC) class 1 molecule antigen presentation.

The Sponsor is in phase 1 and 2 of drug development. In the Clinical Study Report (CSR) for the phase 1/2 study, R5458-ONC-1826, the Sponsor identified five subjects meeting liver analyte criteria for Hy's Law. DHM requested the DHN DILI Team assess these five cases for attribution to LVN. DHM did not request further assessments.

III. Significant Review Findings

1. Phase 1 and 2 trials under study R5458-ONC-1826

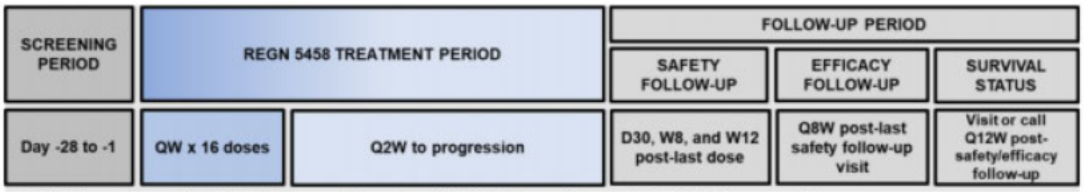
Brief descriptions of the phase 1 and 2 studies with enrollment numbers are in **Table 1** below.[2] As of Nov 20, 2023, 282 subjects were enrolled.

Table 1: Listing of Clinical Studies Supporting the Linvoseltamab Marketing Application

Study ID	Country/ Region	Study design	Study population	Dose Regimen	Primary Objective	Enrollment
R5458-ONC-1826 (Ongoing; Primary CSR)	US, UK, EU, South Korea	Phase 1/2 open-label, FIH study of the safety, tolerability, anti-tumor activity, and PK of linvoseltamab (anti-BCMA x anti-CD3 bispecific antibody)	**Phase 1** Patients with MM who have exhausted all therapeutic options that are expected to provide meaningful clinical benefit. In addition, each patient must have progressed after at least 3 prior lines of therapy, including an anti-CD38 antibody, a PI, and an IMiD OR progression on or after an anti-CD38 antibody and have double-refractory disease (to a PI and IMiD) or intolerance. **Phase 2** Patients must have progressed on or after 3 prior lines of therapy including a PI, IMiD, and anti-CD38 antibody, OR must be triple-refractory (defined as refractory to at least 1 PI, 1 IMiD, and an anti-CD38 monoclonal antibody).	**Phase 1** Dose escalation study to investigate linvoseltamab full dose from 3 mg (DL1) up to 800 mg (DL9) **Phase 2** Dose optimization study with 2 selected doses: Cohort 1: 5 mg/25 mg/50 mg Cohort 2: 5 mg/25 mg/200 mg	**Phase 1** To assess the safety, tolerability, DLTs and to determine one or more RP2DRs of linvoseltamab as monotherapy in patients with RRMM **Phase 2** To assess the anti-tumor activity of linvoseltamab separately in cohorts 1 and 2, as measured by ORR as determined by blinded IRC, as measured using the IMWG criteria.	*Planned Enrollment:* **Phase 1** Up to 83 **Phase 2 Cohort 1** ~104 **Phase 2 Cohort 2** ~104 *Currently Enrolled:* **Phase 1** 73 (complete) **Phase 2 Cohort 1** 104 (complete) **Phase 2 Cohort 2** 105 (complete)

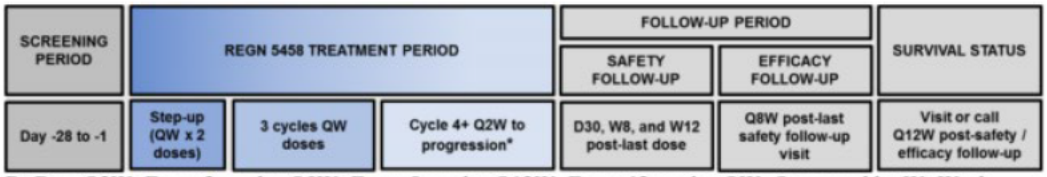
The schematics for phase 1 and 2 studies are shown in the **Figures 1 and 2**.

[1] BLA761400 (761400 - 0031 - (31) - 2024-05-03 - ORIG-1 /Clinical/Response To Information Request) - Introduction (#2)
[2] BLA761400 (761400 - 0024 - (24) - 2024-04-11 - ORIG-1 /Clinical/Response To Information Request) - Tabular Listing of All Clinical Studies (#2)



Q2W=Every 2 weeks; Q8W= Every 8 weeks; Q12W=Every 12 weeks; QW=Once weekly

Figure 1: Study schematic for R5458-ONC-1826, phase 1.[3]



D=Day; Q2W=Every 2 weeks; Q8W=Every 8 weeks; Q12W=Every 12 weeks; QW=Once weekly; W=Week
*Upon discussion between the investigator and the sponsor, patients in cohort 1 who tolerate 50 mg and progress after a minimum of 4 weeks of treatment or a maximum of 12 full doses of treatment (Figure 7), may dose escalate to 200 mg (Section 7.3.1). For patients enrolled in cohort 2 (200 mg full dose) who achieve a response of VGPR or better and have received REGN5458 for a minimum of 24 weeks, the frequency of study drug administration will be decreased from Q2W to Q4W intervals (Figure 8). For patients who undergo intra-patient dose escalation from 50 mg to 200 mg, dosing frequency will be decreased from Q2W to Q4W intervals if they have achieved a response of VGPR or better and have received 200 mg for 24 weeks (Section 7.3.1).

Figure 2: Study schematic for R5458-ONC-1826, phase 2.[4]

2. Case level assessments: The sponsor identified five subjects meeting liver analyte criteria for Hy's Law as of Sep 8, 2023 (data lock for CSR).[5] We assessed all five subjects as unlikely DILI. All five had compelling alternate diagnoses. Because none of the liver injuries were attributable to DILI, none met Hy's Law.

Table 2: Summary of five subjects with liver analyte criteria meeting Hy's Law.[6]

#	ID	Study	Causality Score*	Alternate diagnosis	Age (y)	Sex	Race	Hy's Law
1	(b) (6)	R5458-ONC-1826	5	Tumor lysis syndrome; sepsis	81	F	White	No
2		R5458-ONC-1826	5	Cytokine release syndrome; shock	59	M	Unknown	No
3		R5458-ONC-1826	5	Cytokine release syndrome	58	M	Black AA	No
4		R5458-ONC-1826	5	Shock, sepsis	60	F	White	No
5		R5458-ONC-1826	5	Cytokine release syndrome	67	F	White	No

*1=definite, 2=highly likely, 3=probable, 4=possible, **5=unlikely**, 6=indeterminate

[3] BLA761400 (761400 - 0024 - (24) - 2024-04-11 - ORIG-1 /Clinical/Response To Information Request) - Protocol Amendment 9 US (#103)
[4] BLA761400 (761400 - 0024 - (24) - 2024-04-11 - ORIG-1 /Clinical/Response To Information Request) - Protocol Amendment 9 US (#110)
[5] BLA761400 (761400 - 0026 - (26) - 2024-04-15 - ORIG-1 /Clinical/Response To Information Request) - Study Report (#248)
[6] Made by DILI Team

IV. Conclusions

None of the cases of concern for meeting Hy's Law were due to DILI. Therefore, there were no Hy's Law cases. All five had clear and compelling non-DILI reasons to have liver analytes increase (e.g., tumor lysis) or to have liver damage (e.g., shock, cytokine release syndrome). Based on these data, there are no Hy's Law cases that would suggest need for clinical hold.

In this limited consult, we did not review non-clinical data or aggregate clinical data for liver injury (e.g., animal studies, eDISH plots, shift tables), and we relied on the Sponsor's identification of cases concerning for Hy's Law cases (i.e., cases of concern for substantial DILI risk).

V. Recommendations

None.

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Abbreviations:

BCMA: B cell maturation antigen
DILI: drug-induced liver injury
LNV: linvoseltamab

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/s/

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