CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761291Orig1s000

OTHER REVIEW(S)

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:	August 15, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761291
Product Name and Strength:	Tecvayli (teclistamab-cqyv) Injection, 30 mg/3 mL (10 mg/mL) and 153 mg/1.7 mL (90 mg/mL)
Applicant/Sponsor Name:	Janssen Biotech, Inc.
OSE RCM #:	2021-2486-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on August 5, 2022 for Tecvayli. We reviewed the revised carton labeling for Tecvayli (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] These revisions are also in response to recommendations that were sent to the Applicant regarding revised container labels and carton labeling submitted on July 22, 2022. We note the Applicant indicated it is not possible to relocate the mock-up number because this location is a condition of the camera set-up on the packaging line.

2 CONCLUSION

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

[a] Iverson, N and Labeling Review for Tecvayli (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUN 28. RCM No.: 2021-2486.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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HINA S MEHTA
08/22/2022 02:10:13 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:	August 19, 2022
To:	Denise Felluca, PharmD, MBA 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)**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jennifer Chen, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling:
Drug Name (proper name):	TECVAYLI (teclistamab-cqyv)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761291
Applicant:	Janssen Biotech, Inc. c/o Janssen Research & Development, LLC

1 INTRODUCTION

On December 28, 2021, Janssen Biotech, Inc. c/o Janssen Research & Development, LLC submitted for the Agency's review an original Biologics License Application (BLA) 761291 for TECVAYLI (teclistamab-cqyv) injection to seek approval for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD-38 monoclonal antibody.

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 28, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TECVAYLI (teclistamab-cqyv) injection.

2 MATERIAL REVIEWED

- Draft TECVAYLI (teclistamab-cqyv) injection MG received on December 28, 2021, and downloaded from SharePoint by DMPP on August 8, 2022.
- Draft TECVAYLI (teclistamab-cqyv) injection Prescribing Information (PI) received on December 28, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on August 4, 2022 and August 18, 2022.

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 Prescribing Information (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/

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LASHAWN M GRIFFITHS
08/19/2022 01:16:25 PM

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

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

Memorandum

Date: 8/17/22

To: Denise Felluca, PharmD, MBA, Regulatory Health Project Manager, Division of Hematologic Malignancies II (DHM2)

From: Jennifer Chen, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Subject: OPDP Labeling Comments for TECVAYLI™ (teclistamab-cqyv) injection, for subcutaneous use

BLA: 761291

In response to DHM2's consult request dated January 28, 2022, OPDP has reviewed the proposed product labeling (PI) and Medication Guide (MG) for the original BLA submission for TECVAYLI™ (teclistamab-cqyv) injection, for subcutaneous use.

Labeling: OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DHM2 (Denise Felluca) on August 15, 2022, and are provided below.

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

Thank you for your consult. If you have any questions, please contact Jennifer Chen at (301) 796-9398 or Jennifer.Chen@fda.hhs.gov.

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LABL 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:	June 28, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761291
Product Name, Dosage Form, and Strength:	Tecvayli (teclistamab-cqyv) Injection, 30 mg/3 mL (10 mg/mL) and 153 mg/1.7 mL (90 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Janssen Biotech, Inc.
FDA Received Date:	December 28, 2021 and January 25, 2022
OSE RCM #:	2021-2486
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Tecvayli (teclistamab-cqyv) Injection, this review evaluates the proposed Tecvayli 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 – N/A
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

Janssen Biotech, Inc. submitted a 351(a) application to obtain marketing approval of Tecvayli (teclistamab-cqyv) Injection. Tecvayli is proposed for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

We performed a risk assessment of the proposed container labels, carton labeling, PI, and Medication Guide for Tecvayli Injection to determine whether there are significant concerns in terms of safety related to preventable medication errors. We note the PI states patients should (b) (4) Patients need to be monitored due to the

risk of cytokine release syndrome. 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. The clinical team responded and stated patients will be required inpatient hospitalization for at least 48 hours after each step-up dose and the first full treatment dose as this was what was done in the study protocol. We defer to the clinical team for revisions to that part of the PI.

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 preparation instructions lack clarity, the product strength is not in accordance with USP General Chapter <7>, Labeling, the strength appears as a large number without a comma, trailing zeroes, dangerous abbreviations and symbols . Furthermore, we also note the placeholders "TRADENAME" and "teclistamab-xxxx" should be replaced with the conditionally acceptable proprietary and non-proprietary names, "Tecvayli (teclistamab-cqyv)". For the Applicant, we note that the Rx only statement is missing on the 153 mg/1.7 mL container label vial and appears prominent on the 30 mg/3 mL container label vial and all carton labeling. In addition, the placeholders "TRADENAME" and "teclistamab-xxxx" should be replaced with the conditionally acceptable proprietary and non-proprietary names, "Tecvayli (teclistamab-cqyv)" on the labels and labeling. 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 Janssen Biotech, Inc. to address our concerns.

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

A. Highlights of Prescribing Information

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, Tecvayli.
2. As currently presented, the nonproprietary name is denoted by the placeholder "teclistamab-xxxx". Replace all presentations of the placeholder "teclistamab-xxxx" with the conditionally acceptable nonproprietary name, teclistamab-cqyv.

3. The route of administration is missing; therefore we recommend including the statement, "Administer by subcutaneous injection only" as the first bullet in the Dosage and Administration Section of Highlights of Prescribing Information.

4. Tecvayli Injection has different preparation instructions depending upon the patient's actual body weight and recommended dosage. Therefore, we recommend including the statement, "See Full Prescribing Information for instructions on preparation and administration. (2.5)."

B. Full Prescribing Information

1. Dosage and Administration Section

a. Section Recommended Dosage

i. We recommend revising the statement, "Administer pretreatment medications prior to each dose of the TRADENAME step-up dosing schedule *[see Dosage and Administration (2.2)]*." to "Administer pretreatment medications prior to each dose of the TRADENAME step-up dosing schedule, which includes step-up dose 1, step-up dose 2, and the first treatment dose as described in Table 1 *[see Dosage and Administration (2.2)]*." for added clarity.

b. Section 2.2 Recommended Pretreatment Medications

i. We recommend revising the first statement as, "Administer the following pretreatment medications 1 to 3 hours before each dose of the TRADENAME step-up dosing schedule which includes step-up dose 1, step-up dose 2, and the first treatment dose (see Table 1), including when step-up dosing is repeated following a dose delay to reduce the risk of cytokine release syndrome *[see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)]*."

ii. The strength of acetaminophen and methylprednisolone are presented as large numbers and appears without comma(s) to improve readability. 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 strength statement of acetaminophen and methylprednisolone to include a comma, for example, to read as 1,000 instead of 1000 throughout the Prescribing Information.

c. Section 2.3 Dosage Modifications

   i. We recommend deleting the statement, (b) (4) , as this information is not needed.

   ii. The laboratory values are presented with a trailing zero (e.g., 1.0 x 10^9/L), which can lead to tenfold misinterpretations. We recommend revising the laboratory values to remove all trailing zeroes.

   iii. In the Table 2, Recommended Actions taken for Adverse Reactions Following Administration of TRADENAME, the unit of measure for the platelet count is presented with an error prone symbol, "µL". Certain symbols should not be used in labeling as they can be misinterpreted. Therefore, we recommend revising the unit of measure for the platelet count from, "µL" to "mcL".

d. Section 2.4 Management of Severe Adverse Reactions

   i. We recommend revising the statement, "Administer supportive care for CRS (including, but not limited to, anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) as appropriate." to "Administer supportive care for CRS (including, but not limited to, anti-pyretic agents, intravenous fluid support, vasopressors, supplemental oxygen, etc.) as appropriate." to remove the abbreviation and for clarity.

   ii. As currently presented, Table 4: Recommendations for Management of Cytokine Release Syndrome with Tocilizumab and Corticosteroids and Table 5: Recommendations for Management of Immune Effector Cell-Associated Neurotoxicity Syndrome contains the symbols, "≥", "≤", and ">". We recommend replacing the symbols, "≥", "≤", and ">" with the intended meanings.

e. Section 2.5 Administration

   i. We recommend revising the title of Section 2.5 "Administration" to Section 2.5 "Preparation and Administration" as it contains preparation and administration instructions.

   ii. We recommend deleting the first sentence, (b) (4) as this information is not needed.

iii. We recommend revising the statement, "TRADENAME should be administered via subcutaneous injection only." To "TECVAYLI is intended for subcutaneous use by a healthcare professional only." for added clarity.

iv. The product strengths are not expressed as a total quantity per total volume followed by the concentration per mL. The product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling. We recommend revising the strength statements, "10 mg/mL" and "90 mg/mL" to "30 mg/3 mL (10 mg/mL) and "153 mg/1.7 mL (90 mg/mL)" in accordance with USP General Chapter <7>, Labeling.

v. The warning statement (b) (4) is expressed as a negative statement. Post-marketing reports have shown that negative statements (b) (4) may have the opposite of the intended meaning because the word (b) (4) can be overlooked and misinterpreted as an affirmative action. We recommend deleting the statement (b) (4) as the route of administration is expressed using a positive statement, "TRADENAME should be administered via subcutaneous injection only.".

vi. We recommend deleting Tables 6, 7, and 8 as this information is not needed since the required injection volume is not specific for each patient body weight in the dosing range.

vii. We recommend revising the statement, "Each injection volume should not exceed 2.0 mL. Divide doses requiring greater than 2.0 mL equally into multiple syringes." to remove the trailing zeroes.

viii. We recommend revising the statement, "If TRADENAME is not used immediately, store refrigerated at 2-8°C or at ambient temperature for a maximum of 20 hours. Discard after 20 hours, if not used." to "If TECVAYLI is not used immediately, store refrigerated at 2 to 8°C or at ambient temperature for a maximum of 20 hours. Discard after 20 hours, if not used." for added clarity.

2. How Supplied/Storage and Handling Section

a. The product strengths are not expressed as a total quantity per total volume followed by the concentration per mL. The product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling. We recommend revising the strength statements, "One 30 mg/3 mL single-dose vial in a carton" and "One 153 mg/1.7 mL single-dose vial in a carton" to " One 30 mg/3 mL (10 mg/mL) single-dose vial in a carton" and "One 153 mg/1.7 mL (90 mg/mL) single-dose vial in a carton" in accordance with USP General Chapter <7>, Labeling.

C. 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, Tecvayli.
2. As currently presented, the nonproprietary name is denoted by the placeholder "teclistamab-xxxx". Replace all presentations of the placeholder "teclistamab-xxxx" with the conditionally acceptable nonproprietary name, teclistamab-cqyv.

4.2 RECOMMENDATIONS FOR JANSSEN BIOTECH, 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, Tecvayli.
2. As currently presented, the nonproprietary name is denoted by the placeholder "teclistamab-xxxx". Replace all presentations of the placeholder "teclistamab-xxxx" with the conditionally acceptable nonproprietary name, teclistamab-cqyv.
3. The Rx Only statement appears prominent on the principal display panel. Decrease the prominence by debolding the Rx Only statement.

B. Container Label 30 mg/ 3 mL

1. As currently presented, the code, [redacted] (b) (4) " is located in close proximity to the lot number, which could lead to confusion. Numbers or codes located in close proximity to the lot number may be mistaken as the lot number. We recommend deleting or relocating the code, [redacted] (b) (4)

C. Container Label 153 mg/1.7 mL

1. Add an non-bolded Rx only statement to the 153 mg/1.7 mL vial label.

2. Add the required manufacturer's name to the 153 mg/1.7 mL vial label and if space permits add the US license number.

D. 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 subcutaneous Use" to read "For subcutaneous injection 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.
2. We recommend removing the statements, (b) (4) from the carton labeling as it implies the entire vial will be needed for the dose. Since this product requires weight-based dosing, the entire vial may not be needed for required dose.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tecvayli received on January 28, 2022 from Janssen Biotech, Inc..

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Tecvayli</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Nonproprietary Name</td><td>teclistamab-cqyv</td></tr>
<tr><td>Indication</td><td>For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.</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>30 mg/3 mL (10 mg/mL) and 153 mg/1.7 mL (90 mg/mL)</td></tr>
<tr><td>Dose and Frequency</td><td>
<table>
<tr><th colspan="3">Step-up Dosing Schedule</th></tr>
<tr><th></th><th>TRADENAME Dose*</th><th>Dose Schedule</th></tr>
<tr><td>Step-up Dose 1</td><td>0.06 mg/kg</td><td>First day of treatment</td></tr>
<tr><td>Step-up Dose 2</td><td>0.3 mg/kg</td><td>Two to four days after Step-up Dose 1</td></tr>
<tr><td>Treatment Dose</td><td>1.5 mg/kg</td><td>Two to four days after Step-up Dose 2</td></tr>
<tr><td colspan="3">* Dose is based on actual body weight and should be administered subcutaneously.</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>• One 30 mg/3 mL single-dose vial in a carton
• One 153 mg/1.7 mL single-dose vial in a carton</td></tr>
<tr><td>Storage</td><td>Store refrigerated at 2°C to 8°C (36°F to 46°F). Store in the original carton to protect from light. Do not freeze.</td></tr>
</table>

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,[a] along with postmarket medication error data, we reviewed the following Tecvayli labels and labeling submitted by Janssen Biotech, Inc..

- Container labels received on December 28, 2021
- Carton labeling received on December 28, 2021
- Prescribing Information (Image not shown) received on January 28, 2022, available from \\CDSESUB1\evsprod\bla761291\0004\m1\us\draft-labeling-text.pdf
- Medication Guide received on January 28, 2022, available from \\CDSESUB1\evsprod\bla761291\0004\m1\us\draft-labeling-text-usmg.doc

G.2 Label and Labeling Images

Container labels

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

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CLINICAL INSPECTION SUMMARY

Date	April 22, 2022
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Acting Branch Chief/ Division Director Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Elizabeth Hill, MD, Medical Officer Bindu Kanapuru, M.D., Medical Team Leader Nicole Gormley, M.D., Division Director Denise Felluca, Pharm.D., Regulatory Health Project Manager Division of Hematology Malignancies 2 (DHM2) Office of Oncology Drugs
BLA	BLA 761291
Applicant	Janssen Biotech, Inc., subsidiary of Janssen Research and Development, LLC.
Drug	Tecvayli™ (teclistamab)
NME	Yes
Division Classification	Ig G4 immunoglobulin bispecific B cell maturation antigen directed- and CD3-directed antibody
Proposed Indication	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody
Review Type	Priority Review (Breakthrough Therapy)
Consultation Request Date	January 28, 2022
Summary Goal Date	April 28, 2022
Action Goal Date	June 28, 2022
PDUFA Date	August 28, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study 64007957MMY1001(referred in this document as Study 1001) were submitted to the Agency in support of a Biologics LicenseApplication (BLA) for the drug teclistamab, proposed as treatment of adult patients with relapsed or refractory multiple myeloma. Two clinical investigators (Alfred Garfall, M.D. and Amrita Krishnan, M.D.) were inspected, sponsored by Janssen Biotech, Inc., subsidiary of Janssen Research and Development, LLC, a component of Janssen Pharmaceutical Companies of Johnson & Johnson.

The study data derived from the above two clinical investigator sites are considered reliable. The study data submitted to the Agency for assessment appeared acceptable in support of the proposed indication.

II. BACKGROUND

Teclistamab is a bispecific B cell maturation antigen (BCMA)-directed and CD3-directed antibody. Bispecific B cell maturation antigen is a cell surface antigen highly expressed on cells of the B cell lineage. The selective expression and the biological importance for the proliferation and survival of myeloma cells makes this antibody a promising target. Teclistamab is a novel immunoglobulin (Ig)G4-4 proline, alanine, alanine (PAA) bispecific antibody protein that binds the CD3 receptor complex on T lymphocytes (T cells) and BCMA on plasma cells, mediating T cell activation and subsequent lysis of BCMA+ cells.

Teclistamab is proposed for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

Under the PDUFA program review, CDER DHM2 requested two large enrolling clinical site inspections for Study 64007957MMY1001.

Study 64007957MMY1001

Study 64007957MMY1001 was a Phase 1 or 2, single-arm, open-label, multicenter study of teclistamab administered as monotherapy to adult subjects with relapsed or refractory multiple myeloma. Phase 1, which included Part 1 (dose escalation) and Part 2 (dose expansion), was intended to evaluate safety and pharmacodynamics of teclistamab, as well as selection and preliminary evaluation of proposed recommended Phase 2 doses [RP2D(s)].

In Part 1, treatment with teclistamab started with intravenous dosing every two weeks and dosing frequency was switched to weekly. After review of safety and efficacy data and considering the greater convenience of subcutaneous administration for patients and healthcare providers, the sponsor amended the protocol to evaluate subcutaneous administration. Dose escalation continued in parallel for both routes of administration.

In Phase 2 (Part 3), the dose level and schedule selected as recommended Phase 2 dose in Phase 1 was evaluated in cohorts of subjects with relapsed or refractory multiple myeloma with unmet medical need. In the primary analysis, data were analyzed for subjects treated at recommended Phase 2 dose for registrational purposes (i.e., subjects treated at 1.5 mg/kg subcutaneous weekly [recommended Phase 2 dose] in Phase 1 and all subjects treated in Cohort A in Phase 2), subjects treated in Phase 1 (dose escalation/dose expansion), and subjects treated in Cohort C (with prior anti-BCMA therapy e.g., idecabtagene).

The primary objectives for this 3-part study were as follows:

Part 1 (Dose Escalation): To identify the proposed recommended Phase 2 dose) and schedule assessed to be safe for teclistamab.
Part 2 (Dose Expansion): To characterize the safety and tolerability of teclistamab at the proposed recommended Phase 2 doses, and
Part 3 (Phase 2): To evaluate the efficacy of teclistamab at recommended Phase 2 doses.

The primary efficacy endpoint for this relapsed/refractory multiple myeloma who previously received at least (b) (4) prior lines of therapy and were triple-drug class exposed was treatment response and teclistamab activity.

This study was conducted at 39 centers that treated at least 1 subject in Belgium (2), Canada (4), France (6), Germany (3), Italy (2), Netherlands (1), Spain (7), Sweden (3), the United Kingdom (3), and the United States (8). A total of 165 subjects were included in the recommended Phase 2 dose main study cohort. The date the first subject signed informed consent was June 8, 2017. This study is ongoing. The date of last observation for last subject recorded as part of the database for primary analysis for the submission was September 7, 2021.

III. RESULTS (by site)

1. **Alfred Garfall, M.D. /Study 64007957MMY1001/Site US 10004**
   Abramson Cancer Center, Perelman Center for Advanced Medicine
   3400 Civic Center Boulevard, 2nd Floor
   Philadelphia, PA 19104

   Inspection dates: February 14 – 18, 2022

   For this study, 60 subjects were consented and screened, 45 subjects were enrolled (including a single transfer study participant from another study site) who received study treatment. There were 22 patients who discontinued due to disease progression, two subjects died, three subjects discontinued due to adverse events, and one study participant was discontinued by the principal investigator due to lack of efficacy. Of the enrolled study subjects, 17 participants remain on treatment for this ongoing study.

   Study files assessed included a review of the Institutional Review Board approvals and informed consent documentation, delegation log, screening and enrollment log, monitoring log and monitoring reports, case report forms, and test article control records. The site audit also involved an evaluation of subject source records medical history, progress notes, laboratory results, blood sample records, ancillary procedures, imaging records and reports, adverse event and serious adverse event documentation, and subject-specific protocol deviation records.

   Source records were reviewed for ten enrolled subjects. The reviewed source records included medical history, eligibility criteria, randomization, protocol-required procedures, adverse events, serious adverse events. No under-reporting of adverse events was found.

Source records for the enrolled study patients were examined and verifiable for primary efficacy data against the data line listings, including the investigator's response assessment and independent review committee as part of the endpoint data. No discrepancies were noted.

2. Amrita Krishnan, M.D./ Study 64007957MMY1001 /Site US 10005
1500 E. Duarte Rd
Duarte, CA 91010

Inspection dates: February 28 to March 4, 2022

For Study 64007957MMY1001, a total 73 patients were screened, and 37 subjects were enrolled. Of the 37 enrolled participants, 21 study subjects received treatment. Of the 21 subjects who were treated on-study: 15 study subjects developed progressive disease, one patient died, one patient developed an adverse event leading to study discontinuation, and two were withdrawn from the study by the principal investigator.

The following regulatory documents were assessed: IRB approval letters and correspondence, monitoring reports, informed consent forms, subject medical records, financial disclosure reports, case report forms, subject questionnaires and diaries, dosing records, scans, independent reviewer imaging, site signature and responsibility logs, and site training documentation. The selected subjects' records were audited for eligibility, treatment assignment, blinding and disposition, genetic and laboratory samples and analyzes, protocol adherence, adverse event reporting, efficacy data, and concomitant medications.

A review of all 37 subjects' records was conducted for subjects who completed the informed consent forms. Nine subjects' source records were evaluated for study inclusionary and exclusionary eligibility criteria, adverse events and primary study endpoints.

Source records evaluated, as described, for the nine enrolled study patients were examined and verifiable for primary endpoint data against the data line listings. No discrepancies were noted. There was no evidence of under-reporting of serious adverse events.

While no list of inspectional observations (Form FDA 483) was issued by FDA at the close-out of the inspection site audit, FDA inspector discussed at clinical site close out meeting about adverse events in two subjects that were not captured in the electronic case report form (eCRF) and in the patient data listings. Subject (b) (6) had a mild diarrhea episode concomitant with a hospital stay with neutropenia that resolved uneventfully. Subject (b) (6) reported nausea lasting for three days that eventually resolved but not in the electronic case report form. Although these adverse events should be reported and captured in eCRFs, these episodes were considered to be isolated, and unlikely to have significant impact on the overall safety profiles of the study drug.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Division Director, Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/

ANTHONY J ORENCIA
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MIN LU
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KASSA AYALEW
04/28/2022 09:42:23 AM