

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761444Orig1s000

761444Orig2s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	August 19, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761444
Product Name, Dosage Form, and Strength:	Bilprevda (denosumab-nxxp) injection, 120 mg/1.7 mL (70 mg/mL)
Applicant Name:	Shanghai Henlius Biotech, Inc. (Henlius)
FDA Received Date:	July 30, 2025
TTT ID #:	2024-10712-2
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Shanghai Henlius Biotech, Inc. (Henlius) submitted revised carton labeling received on July 30, 2025 for Bilprevda. The Division of General Endocrinology (DGE) requested that we review the revised carton labeling for Bilprevda (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Shanghai Henlius Biotech, Inc. (Henlius) implemented all of our recommendations and we have no additional recommendations at this time.

^a Rahbani P. Review of Revised Label and Labeling for Bilprevda (BLA 761444). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 July 22. TTT ID: 2024-10712-1.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JULY 30, 2025

Carton Labeling:



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/s/

PEGGY M RAHBANI
08/19/2025 09:33:46 AM

YEVGENIYA M KOGAN
08/19/2025 09:58:02 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	August 19, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761444
Product Name, Dosage Form, and Strength:	Bildyos (denosumab-nxxp) injection, 60 mg/mL
Applicant Name:	Shanghai Henlius Biotech, Inc. (Henlius)
FDA Received Date:	July 30, 2025
TTT ID #:	2024-10711-2
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Shanghai Henlius Biotech, Inc. submitted revised carton labeling received on July 30, 2025 for BILDYOS. The Division of General Endocrinology (DGE) requested that we review the revised carton labeling for BILDYOS (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Shanghai Henlius Biotech, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

^a Rahbani P. Review of Revised Label and Labeling for BILDYOS (BLA 761444). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 Jul 22. TTT ID: 2024-10711-1.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JULY 30, 2025

Carton Labeling:

(b) (4)



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/s/

PEGGY M RAHBANI
08/19/2025 09:29:27 AM

YEVGENIYA M KOGAN
08/19/2025 09:56:50 AM

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

PATIENT LABELING REVIEW

Date: July 29, 2025

To: Alice Lee, PharmD
Regulatory Project Manager
Division of General Endocrinology (DGE)

Through: Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon Williams, MSN, BSN, RN
Patient Labeling Reviewer Position Title
Division of Medical Policy Programs (DMPP)

Meena Savani
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name
(nonproprietary name): Bildyos (denosumab-nxxp)¹

Dosage Form and
Route: injection, for subcutaneous use

Application
Type/Number: BLA 761444

Applicant: Shanghai Henlius Biotech, Inc.

¹ Bildyos has been developed as a proposed biosimilar to US-licensed Prolia (denosumab). The proposed proprietary name Bildyos and nonproprietary name suffix-nxxp were found to be conditionally acceptable on May 25, 2025 by the Division of Medication Error Prevention and Analysis I (DMEPA 1).

1 INTRODUCTION

On August 30, 2024, Shanghai Henlius Biotech., submitted for the Agency's review a New Biologics License Application (BLA) 761444 for Bıldıys (denosumab-nxxp) injection, for subcutaneous use a biosimilar to US-licensed PROLIA (denosumab), injection for subcutaneous use (BLA 125320).

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 General Endocrinology (DGE) on October 22, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for Bıldıys (denosumab-nxxp) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft Bıldıys (denosumab-nxxp) MG received by DMPP and OPDP on August 30, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 21, 2025.
- Draft Bıldıys (denosumab-nxxp) Prescribing Information (PI) received on August 30, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 21, 2025.
- Prolia (denosumab) MG approved May 30, 2025.

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)
- ensured that the MG is consistent with the approved 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.

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

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/s/

SHARON W WILLIAMS
07/29/2025 01:27:03 PM

MEENA R SAVANI
07/29/2025 02:25:02 PM

MARCIA B WILLIAMS
07/29/2025 02:26:43 PM

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

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

Memorandum

Date: July 25, 2025

To: Alice Lee, PharmD, Regulatory Project Manager
Division of General Endocrinology Products (DGE)

LaiMing Lee, Associate Director for Labeling (DGE)

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for BILDYOS (denosumab-xxxx) injection, for subcutaneous use

BLA: 761444

Background:

In response to DGE's consult request dated October 22, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original BLA submission for BILDYOS (denosumab-xxxx) injection, for subcutaneous use.

PI and Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on July 24, 2025, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review for the BILDYOS Medication Guide 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 submitted to the electronic document room on July 18, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

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/s/

MEENA R SAVANI
07/25/2025 02:21:09 PM

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

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

Memorandum

Date: July 22, 2025

To: Alice Lee, PharmD, Regulatory Project Manager
Division of General Endocrinology Products (DGE)

LaiMing Lee, PhD, Associate Director for Labeling, DGE

From: Jeena Sun, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for BILPREVDA (denosumab-xxxx) injection,
for subcutaneous use

BLA: 761444

Background:

In response to DGE's consult request dated October 22, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original BLA submission for BILPREVDA (denosumab-xxxx) injection, for subcutaneous use.

PI:

OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on July 21, 2025, and we do not have any comments at this time.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on July 18, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Jeena Sun at (301) 796-9699 or Jeena.Sun@fda.hhs.gov.

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/s/

JEENA L SUN
07/22/2025 05:15:40 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	July 22, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761444
Product Name, Dosage Form, and Strength:	Bilprevda (denosumab-nxxp) injection, 120 mg/1.7 mL (70 mg/mL)
Applicant Name:	Shanghai Henlius Biotech, Inc. (Henlius)
FDA Received Date:	July 18, 2025
TTT ID #:	2024-10712-1
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Shanghai Henlius Biotech, Inc. submitted revised container label and carton labeling received on July 18, 2025 for Bilprevda. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Bilprevda (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Shanghai Henlius Biotech, Inc. implemented all of our recommendations for the container label and we have no additional recommendations at this time. However, the revised carton labeling is unacceptable 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 Shanghai Henlius Biotech, Inc. in Section 3.

3 RECOMMENDATIONS FOR SHANGHAI HENLIUS BIOTECH, INC.

A. Carton Labeling

1. We note you added a (b) (4) statement on the principal display panel (PDP). (b) (4) We recommend that you delete (b) (4) statement on the PDP.
2. As currently presented, (b) (4) Consider removing (b) (4)
3. On the Principal Display Panel (PDP) the net quantity statement appears more prominent than other important information. We recommend you consider relocating the net quantity statement below the statement “Bilprevda should be administered by healthcare provider”.
4. On the side panel, the net quantity is presented as:
(b) (4)
Adjust the formatting so that the net quantity statement appears (b) (4) to improve readability.

^a Rahbani P. Label and Labeling Review for Bilprevda (BLA 761444). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 Jun 27. TTT ID: 2024-10712.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JULY 18, 2025

Container Label:



(b) (4)

Carton Labeling:

(b) (4)



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/s/

PEGGY M RAHBANI
07/22/2025 08:51:07 AM

YEVGENIYA M KOGAN
07/22/2025 10:36:35 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	July 22, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761444
Product Name, Dosage Form, and Strength:	Bildyos (denosumab-nxxp) injection, 60 mg/mL
Applicant Name:	Shanghai Henlius Biotech, Inc. (Henlius)
FDA Received Date:	July 18, 2025
TTT ID #:	2024-10711-1
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Shanghai Henlius Biotech, Inc. submitted revised container labels and carton labeling received on July 18, 2025, for Bildyos. The Division of General Endocrinology (DGE) requested that we review the revised container labels and carton labeling for Bildyos (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Shanghai Henlius Biotech, Inc. implemented all of our recommendations for the container labels, and we have no additional recommendations at this time. However, the revised carton labeling are unacceptable 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 Shanghai Henlius Biotech, Inc. in Section 3.

3 RECOMMENDATIONS FOR SHANGHAI HENLIUS BIOTECH, INC.

A. Carton Labeling

1. On the Principal Display Panel (PDP) the net quantity statement appears more prominent than other important information. We recommend you consider relocating the net quantity statement below the statement “Bildyos should be administered by healthcare provider”.
2. Prefilled Syringe Carton Labeling and Vial Carton Labeling:
 - a. As currently presented the Medication Guide (MG) statement does not appear prominent and conspicuous on the Principal Display Panel (PDP). Revise the Medication Guide statement on the PDP in accordance with 21 CFR 208.24(d). You may consider putting a box around the statement.

3. Vial Carton Labeling:

- a. As currently presented,  (b) (4)

Consider removing  (b) (4)


4. Vial Carton Labeling:

- a. On the side panel, the net quantity is presented as:

 (b) (4)

^a Rahbani P. Label and Labeling Review for Bildyos (denosumab-nxxp). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 Jun 27. TTT ID: 2024-10711

Adjust the formatting so that the net quantity statement appears to improve readability.

(b) (4)

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JULY 18, 2025

Container Labels:



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/s/

PEGGY M RAHBANI
07/22/2025 08:43:47 AM

YEVGENIYA M KOGAN
07/22/2025 10:35:03 AM

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: July 10, 2025

TO: Theresa Kehoe, M.D.
Director
Division of General Endocrinology (DGE)
Office of Cardiology, Hematology, Endocrinology and
Nephrology (OCHEN)
Office of New Drugs (OND)

FROM: Makini Cobourne-Duval, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Review of Clinical Inspection of Wuxi People's
Hospital, Wuxi, China

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of study HLX14-001 conducted at Wuxi People's Hospital, Wuxi, China under BLA 761444 and IND 153872.

Objectionable conditions were found during the inspection and Form FDA 483 was issued at the inspection close-out. There was also one discussion item addressed at the close of the inspection. After reviewing the inspectional findings, the exhibits provided in EIR, and the CI's response to Form FDA 483 and the discussion item, OSIS has concerns regarding the safeguarding the rights and welfare of human subjects, specifically with respect to the site's provision of false information during the medical counseling of a subject and his partner, which appears to have resulted in termination of a pregnancy conceived during the subject's participation of the study. OSIS also concluded there were two regulatory violations under 21 CFR 312. However, the observations and discussion item do not impact the reliability of the data for inspected study HLX14-001.

2. Inspected Study:

BLA 761444

Study Number: HLX14-001

Study Title: "A Randomized, Parallel, Single-dose, Subcutaneous Injection, Phase I Clinical Study of HLX14 versus Prolia® (Denosumab) in Chinese Healthy Adult Male Subjects for Comparison in Pharmacokinetic Characteristics, Safety, and Immunogenicity"

Dates of study conduct: 11/20/2020 - 9/12/2023

Clinical Investigator: Kai Huang, Ph.D.

Clinical site: Wuxi People's Hospital
299 Qingyang Road, Nanchang District
Wuxi, Jiangsu, China

3. Inspectional Findings

Wuxi People's Hospital, Wuxi, China

OII investigator Jennifer C. Adams inspected Kai Huang, Ph.D. at Wuxi People's Hospital, 299 Qingyang Road, Nanchang District, Wuxi, Jiangsu, China from May 12-16, 2025.

3.1 Previous Inspections

This was the first OSIS inspection of both Clinical Investigator Kai Huang, Ph.D., and clinical site Wuxi People's Hospital under the BA/BE program.

3.2 Current Inspection

The current inspection included auditing the following items:

- Relevant facilities, study areas, and equipment records
- Relevant standard operating procedures (SOPs)
- Subject eligibility
- Informed consent process and documentation
- Case report forms (CRFs) & study source records
- Protocol compliance
- Ethics Committee approvals
- Investigational product accountability, storage, and reserves
- Blinding
- Randomization & Dosing
- PK sample collection, processing, storage, and shipment
- Adverse event reporting
- Concomitant medication records

3.3 Inspection findings

At the conclusion of the inspection, investigator Jennifer C. Adams observed objectionable conditions and Form FDA 483 was issued to the clinical investigator (CI), Kai Huang, Ph.D. There was also one discussion item addressed at the inspection close-out. The Form FDA 483 observations (**Attachment 1**), the discussion item, the CI's response to the observations (dated 5/30/2025; **Attachment 2**) and discussion item (per the EIR), and my evaluations are presented below.

3.3.1 FDA 483 Observations (written verbatim)

Observation 1:

Failure to perform a clinical study in accordance with good clinical practices. Specifically:

The study HLX14-001 protocol required housing of subjects from Day -1 (pre-dose) through Day 3 (48 hr post-dose), at which point they were to be discharged home for ambulatory visits. You extended housing for subjects in Group 2 and Group 3 from Day 3 through Day 18 (408 hr post-dose) at your facility due to COVID-19 lockdown policies. Although you stated that the extended housing was voluntary, 35 of 36 subjects in Group 2 and 37 of 37 subjects in Group 3 were housed for some time period between Day 3 and Day 18. If not for their participation in study HLX14-001, subjects would not have been housed at your facility during this time frame.

*This systematic change in the protocol was not reported as a protocol deviation to your Ethics Committee. Although the sponsor was aware of the extension to subject housing, it was not reported as a protocol deviation. Study records for subject visits during this time frame conflict with the actual conditions of subject housing on site. For example they indicate that subjects, "returned to the site," for follow-up visits and, were, "permitted to be discharged," when in fact subjects were being housed on-site during this time. **

** text translated from Chinese to English*

You failed to document conditions for subject housing during this extended housing period. For example, you stated that you provided subjects daily COVID-19 NAT tests for at least some of their extended housing, but you did not collect or maintain records of these tests. Of the 37 Group 3 subjects, 17 developed COVID-19 while being housed at your facility or on the day they departed, with 2 more developing COVID-19 within 4 days after their departure. Progress notes for many of these subjects indicate that cohabiting individuals tested positive for COVID-

19; these cohabitating individuals were other subjects also being housed at your facility at that time.

Serious infection is an adverse event of special interest for Study HLX14-001.

OSIS Evaluation:

Because multiple issues were cited within Observation 1, I evaluated each one separately to allow the appropriate parsing of these distinct issues.

- A. The CI/site extended housing up to 14 nights beyond the period outlined in the study protocol for 72 of the 73 subjects from Groups 2 and 3 due to local government COVID-19 lockdown policies and did not report this housing extension as a protocol deviation to their Ethics Committee and/or the Agency. Per protocol, subjects are scheduled to be discharged from the hospital after the blood sample collections, laboratory tests, and examinations at 48-h post-dose timepoint. Furthermore, the protocol states, "Any intentional or unintentional deviation from or violation of the trial protocol and GCP principles are regarded as protocol deviation or protocol violation. Any protocol deviations should be recorded in the unified protocol deviation appendix...". The provided exhibit, "Additional Accommodation List" (**Attachment 3**), confirmed that these subjects remained housed at the clinical facilities beyond the period established in the protocol. Therefore, I conclude that the site's housing extension was a protocol violation and should have been reported as such. However, there is no evidence that the scheduled study activities (e.g., blood sample collections, laboratory tests, and examinations) were compromised during the extended housing period. Additionally, per the EIR, the housing extension was voluntary for subjects, and they were free to return home at their discretion during the extended period. Thus, I conclude this protocol violation had no impact on the integrity of the data.
- B. The site had discrepant documentation of events for several subjects in the study records regarding the subjects' housing at and discharging from the clinical facilities. Specifically, the subjects' progress notes stated/indicated subjects came in for study visits and returned home after each scheduled visit. However, the "Additional Accommodation List" (**Attachment 3**) as well as the CI's account of events during the study (provided during the inspection and documented in the EIR) confirmed that most of the subjects from Groups 2 and 3 remained housed at the clinical site before and after those scheduled site visits. The 21 CFR 312.62 regulations on investigator recordkeeping

and record retention states that an investigator is required to prepare and maintain adequate and accurate case histories that record all observations and data pertinent to the study. The CI/site failed to prepare accurate study records in the progress notes during the extended housing period. The progress notes were recorded as if the subjects were discharging from and returning to the clinical site as planned/expected in the absence of the government lockdown policies triggered by the ongoing public health emergency (i.e., rapid spread of COVID-19). It is apparent that the documentation in the progress notes regarding the discharge and return of multiple subjects for multiple scheduled site visits were not contemporaneous. In addition, the site may have used a templated language for the progress notes as the progress notes for five subjects I reviewed contain exact same languages across the subjects and visits. This documentation in the progress notes did not accurately reflect the conditions/circumstances during the time of study conduct. Therefore, I conclude that Part B of Observation 1 regarding the discrepant documentation is a regulatory violation under 21 CFR 312.62. However, the document discrepancy regarding the subjects' discharging/returning versus remaining housed at the clinical site for an extended period has no impact on data integrity since there is no evidence that the scheduled study activities (e.g., blood sample collections, laboratory tests, and examinations) were compromised.

- C. The CI/site did not collect and maintain the records from the daily COVID-19 nucleic acid tests (NATs) that were, according to the CI, issued to subjects throughout the extended housing period. The protocol states that investigators should record the study-related observation parameters and other data of each subject in the source medical record completely and accurately. The provided exhibits show that the COVID-19 infections were recorded in the progress notes, which also served as source records throughout the study, and were appropriately accounted for within the adverse event listings (16.2.7.1) and reported within the clinical study report as treatment emergent adverse events (TEAEs). Therefore, I conclude this issue cited within Observation 1 is not a protocol violation and has no impact on data integrity.
- D. The CI/site allowed cohabitation of subjects who tested positive for COVID-19 with other housed subjects. The OII investigator also cited that the COVID-19 infections were not reported as adverse events of special interest (AESI), as "serious infection" is defined as an AESI in the protocol. The protocol is silent on procedures or any

required infection-control measures in the event of a contagion. Per the EIR, the CI stated that subjects were housed 3-4 subjects per ward, asked not to gather, and provided one mask per subject per day. I conclude there was no protocol violation concerning the housing conditions/arrangements of the subjects and that it is unlikely the COVID-19 infections impacted PK data.

Regarding the classification and listing of these COVID-19 infections as AESI, the protocol defines an AESI as "hypersensitivity reactions, hypocalcemia, serious infections, osteonecrosis of the jaw, atypical femur fracture, etc." None of the identified COVID-19 cases exceeded Grade 2 in severity, which is defined as "moderate; minimal, local or non-invasive intervention indicated", as assessed by the study investigator. Thus, the identified COVID-19 cases were not classified as "serious infection". Therefore, I conclude that the identified COVID-19 infections were categorized and reported appropriately, and hence this cited issue within Part D of Observation 1 is not a protocol violation, nor does it have any impact on data integrity.

CI's Response:

Several participants from Groups 2 and 3 requested temporary accommodation at the Phase I Clinical Research Center due to: 1) The rapid spread of COVID-19 infections across China in December 2022 and their fear of exposure and, 2) The local (government) COVID-19 policies were rapidly and inconsistently evolving across multiple districts and their concern that their health code could change hence requiring a mandatory ≥ 14 day isolation after leaving the site. The site housed Groups 2 and 3 in different wards separated by floor. The participants were provided voluntary accommodations and meals at no charge and were allowed to depart at their discretion.

A. Regarding the failure to report the extended housing as a protocol deviation, the CI stated that the site's management did not interpret this extension in the housing period as protocol deviation, and therefore did not see the need to report it. After the inspection, the CI recognized and determined that the staff's misinterpretation was due to lack of awareness that any activity outside of the protocol, regardless of rationale, must be considered a deviation, documented, and reported accordingly.

B. Regarding the inconsistency between subjects' progress notes (indicated that subjects were discharged and returned to the site for follow-up visits) and the actual extended housing conditions, the CI stated that they recorded hospitalization and discharge in the progress notes within

the context of the clinical study as defined by the protocol's visit schedule. However, they now understand that not accurately documenting the extended housing in the progress notes was inappropriate. As part of their corrective and preventative actions (CAPA), the site stated they have revised their SOP for Emergency Contingency Plan for Conducting Phase I Clinical Trials During Infectious Disease Outbreaks and Public Health Emergencies and retrained their staff on the revised SOP.

- C. Regarding the COVID-19 testing during the extended stay, the CI stated that subjects took daily COVID-19 NATs as part of the city government's public health policy. These daily COVID tests were conducted independently of the clinical study and the test results were recorded and sent to the subjects via the government's mobile application available through their personal cellphone. The CI confirmed the site did not collect or archive the COVID test results. Per the EIR, the site staff checked the subjects' phones to review test results while they were in extended housing. The COVID-related function of the mobile application was decommissioned, and the local government abruptly discontinued the cellphone app in December 2022. The COVID test result histories for those subjects are no longer accessible. As part of their CAPA, the site stated that all study physicians are required to maintain comprehensive progress notes and source documents including off-site testing reports or certified copies.
- D. Per the CI, to reduce the spread of COVID-19 during the extended housing period, the site implemented infection control measures which included daily ventilation, disinfection, and mask replacement, air purification, and centralized disposal of medical waste. The CI also stated, regarding the categorization of the COVID-19 infections, that all the identified COVID-19 cases that occurred during or shortly after the extended housing period were mild (Grade 1-2) and did not meet the criteria for serious infection i.e., none required hospitalization or had severe clinical outcomes related to the COVID-19 infection.

OBSERVATION 2:

The general requirements for informed consent were not met in that a Commitment Letter which you had Subject (b) (6) and his pregnant partner sign on (b) (6) indicated that the subject and his partner acknowledged that they would bear full responsibility for any consequences resulting from continuing the pregnancy (including all potential outcomes such as fetal malformation), and that the Institute and Sponsor would not be held liable. In addition, progress notes from study visits from*

this date indicate that the study physician told the subject and his partner that: according to the requirements of the trial, they need to terminate pregnancy. On (b) (6) the subject's partner terminated the pregnancy.*

** text translated from Chinese to English*

OSIS Evaluation:

The site had concerning clinical ethics practices and did not appropriately exercise human subject protection during the study via: 1) Incorrectly informing Subject (b) (6) and his partner that they need to terminate a pregnancy conceived during the study period according to the requirements of the study and repeated recommendations to t (b) (6) ct to terminate the pregnancy, and 2) Had Subject (b) (6) and his pregnant partner to sign a Commitment Letter, which had not been previously approved by the IRB, to bear full responsibility for any consequences resulting from continuing the pregnancy. The 21 CFR 312.60 regulation states, "An investigator is responsible for ... protecting the rights, safety, and welfare of subjects under the investigator's care..." According to the translated text from the progress notes and Commitment Letter, the study physician recommended termination of the pregnancy on 2 occasions (b) (6) and, as documented in progress notes (b) (6) communicated false information to the subject regarding the requirements of the clinical study related to the pregnancy. The progress notes dated (b) (6) stated in the translated text, "According to the requirements of the trial, (they/he/she/we) need to terminate pregnancy". The false information told to the subject and his partner that termination of the pregnancy was a study requirement as well as the repeated recommendations from the study physician advising the subject to terminate the pregnancy demonstrate that the site engaged in concerning clinical ethics practices and failed to appropriately exercise human subject protection during study conduct.

Additionally, regarding the Commitment Letter, the protocol states, "The final version of the study protocol, including the final ICF and all other written information and/or material to be provided for subjects, must be approved by the IRB/IEC." The Commitment Letter, which the site had the subject and his partner sign, was not approved by the IRB/IEC and, per the EIR, not valid under Chinese Law according to the site's GCP Office Director. Therefore, I conclude this observation is a violation of the 21 CFR 312.60 regulations as well as the study protocol. Although these violations have no impact on data integrity, OSIS has concerns regarding the site's clinical ethics practices and human subject protection during the study conduct.

** text translated from Chinese to English*

CI's Response:

Per the CI, the study physician (Dr. Lin Zhang) advised that termination of pregnancy could be considered a precaution, but at no point were the participant or his partner coerced, pressured, or unduly influenced into terminating the pregnancy. The CI stated that the subject and his partner voluntarily signed the Commitment Letter for Pregnancy and Informed Consent for Pregnant Partner, and voluntarily terminated the pregnancy.

However, the CI acknowledged that certain statements in the Commitment Letter were inappropriate and did not adequately safeguard the subject's and his partner's rights and autonomy. The CI also acknowledged that the staff's training on the protocol's pregnancy-related procedures was inadequate, resulting in a misinterpretation of its requirements. The CI stated, since receiving the Form FDA 483 inspectional observation, they now understand that the protocol did not mandate or recommend termination of the pregnancy. The staff now recognize that such a recommendation may compromise the subject's autonomy and should not have been documented as a study requirement. The CI acknowledged that the medical note stating, "they need to terminate pregnancy" was inappropriate and poorly phrased because it does not accurately reflect the voluntary nature of the decision.

As part their CAPA, the CI stated that the Commitment Letter has been permanently discontinued. Only the IRB-approved ICF for pregnancy will be used to provide information to study subjects and document consent. Additionally, the site has revised their SOP for handling and reporting of pregnancy event, and the staff received additional training with particular emphasis on the pregnancy-related procedures and the ethical requirements for informed consent.

3.3.2 Discussion Item(s)

Discussion Item 1:

(b) (6) event (sore t (b) (6) progress notes on (b) (6) f (b) (6) cts (b) (6) was removed one week later (b) (6) without explanation/justification.

OSIS Evaluation:

No exhibits were provided in support of this discussion item. Given the nature and relatively isolated occurrence (2 of 102 enrolled subjects) of this issue, I conclude this discussion item has no impact on the integrity of the study data.

Attachments

Attachment 1: Form FDA 483

Attachment 2: Firm's Response to Form FDA 483

Attachment 3: Exhibit 9 - Additional Accommodation List

Makini Cobourne-Duval, Ph.D.
Pharmacologist

Draft: MCD 6/23/2025, 6/24/2025, 6/25/25, 6/26/25, 6/27/25,
6/30/2025, 7/1/2025, 7/2/2025, 7/5/2025, 7/6/2025, 7/7/2025,
7/9/2025, 7/10/2025

Edit: MO 7/9/2025; JC 7/10/2025

OSIS File #: BE 10410

eNSpect Assignment ID: 255547

eNSpect OpID: 306460

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/

MAKINI COBOURNE-DUVAL
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MEI OU
07/10/2025 02:23:48 PM

SEONGEUN CHO
07/10/2025 02:25:40 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 27, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761444
Product Name, Dosage Form, and Strength:	Bildyos (denosumab- nxxp) injection, 60 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Shanghai Henlius Biotech, Inc. (Henlius)
FDA Received Date:	March 14, 2025, and April 14, 2025
TTT ID #:	2024-10711
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 INTRODUCTION

As part of the approval process for BILDYOS (denosumab- nxxp) injection, the Division of General Endocrinology (DGE) requested that we review the proposed BILDYOS Prescribing Information (PI), Medication Guide (MG), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

BILDYOS (denosumab- nxxp) is a proposed 351(k)(4) interchangeable and the US-licensed Reference Product (RP) is PROLIA (denosumab), BLA 125320.

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

3 CONCLUSION

We evaluated the proposed BILDYOS Medication Guide (MG) and Prescribing Information (PI) and determined they are acceptable from a medication error perspective. However, the proposed BILDYOS 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 Endocrinology (DGE) in Section 4 and for Shanghai Henlius Biotech, Inc. in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

Table 2. Identified Issues and Recommendations for the Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	We note a conditionally acceptable nonproprietary name suffix has been approved on May 29, 2025.	Revise the nonproprietary name on all labeling to incorporate the FDA-designated nonproprietary name suffix, “-nxxp”, appended to the core name, “denosumab”, so that the proper name	Replace the suffix placeholder “-xxxx” with the approved suffix “nxxp”.

Table 2. Identified Issues and Recommendations for the Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		appears as “denosumab-nxxp” throughout the labeling. See Draft Guidance for Industry: Nonproprietary Naming of Biological Products: Update (March 2019).	

5 RECOMMENDATIONS FOR SHANGHAI HENLIUS BIOTECH, INC.

Table 3. Identified Issues and Recommendations for Shanghai Henlius Biotech, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	We note a conditionally acceptable nonproprietary name suffix has been approved on May 29, 2025.	Should your BLA be approved during this review cycle, “denosumab- nxxp” will be the proper name designated in the license. Revise the nonproprietary name on all labeling to incorporate the FDA-designated nonproprietary name suffix, “-nxxp”, appended to the core name, “denosumab”, so that the proper name appears as “denosumab-nxxp” throughout the labeling. See Draft Guidance for Industry: Nonproprietary Naming of Biological	Replace the suffix placeholder “-xxxx” with the approved suffix “nxxp”.

Table 3. Identified Issues and Recommendations for Shanghai Henlius Biotech, Inc.
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Products: Update (March 2019).	
2.	Prefilled Syringe: The linear barcode is missing on the syringe container label.	The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2).	Add the product's linear barcode to the syringe container label in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).
3.	Vial Container Label: As currently presented the small size of the container label renders the critical information (e.g., proprietary name, established proper name, strength, etc.) on the label difficult to read.	Per 21 CFR 201.10(i), the small label is required to have the following minimum amount of information: proprietary name, established name, product strength, Identifying lot or control number, name of manufacturer, packer, or distributor, expiration date, and barcode (per 21CFR 201.25(c)(2)).	We recommend increasing the readability of the proprietary name, proper name, and strength by increasing the font size. You may consider removing not minimally required information (e.g., route of administration, "Rx only", and "Single-dose Vial. Discard unused portion, etc.) on the container label.
Prefilled Syringe Blister Label			
1.	We note a conditionally acceptable nonproprietary name suffix has been approved on May 29, 2025.	Should your BLA be approved during this review cycle, "denosumab- nxxp" will be the proper name designated in the license. Revise the nonproprietary name on all labeling to incorporate the FDA-	Replace the suffix placeholder "-xxxx" with the approved suffix "nxxp".

Table 3. Identified Issues and Recommendations for Shanghai Henlius Biotech, Inc.
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		designated nonproprietary name suffix, “-nxxp”, appended to the core name, “denosumab”, so that the proper name appears as “denosumab-nxxp” throughout the labeling.	
2.	As currently presented the storage information does not align with the Prescribing Information (PI). Additionally, the temperature numerical is missing the degree symbol and the storage information lacks prominence.	Storage information should align with the PI. Additionally, lack of clarity and prominence might result in important storage information being overlooked.	Revise the storage information to read “Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Bıldıys must not be exposed to temperatures above 25°C/77°F. Do not freeze. Avoid excessive shaking. Once removed from the refrigerator, Bıldıys must be used within 30 days. Discard Bıldıys if not used within the 30 days. Do not use Bıldıys after the expiry date printed on the label. ”
3.	The manufactured-for name and logo “ORGANON” is located (b) (4)	Due to the (b) (4) logo “ORGANON” it (b) (4) may lead to confusion and medication errors. Furthermore (b) (4) information should not compete in size and prominence with critical information on the principal display panel.	We recommend relocating the (b) (4) logo “ORGANON” (b) (4) such as to the visual space containing storage information. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
Carton Labeling (Vial and Prefilled Syringe)			

Table 3. Identified Issues and Recommendations for Shanghai Henlius Biotech, Inc.
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	We note a conditionally acceptable nonproprietary name suffix has been approved on May 29, 2025.	Should your BLA be approved during this review cycle, “denosumab- nxxp” will be the proper name designated in the license. Revise the nonproprietary name on all labeling to incorporate the FDA-designated nonproprietary name suffix, “-nxxp”, appended to the core name, “denosumab”, so that the proper name appears as “denosumab-nxxp” throughout the labeling. See Draft Guidance for Industry: Nonproprietary Naming of Biological Products: Update (March 2019).	Replace the suffix placeholder “-xxxx” with the approved suffix “nxxp”.
2.	The manufactured-for name and logo “ORGANON” is located (b) (4)	Due to the (b) (4) logo “ORGANON” it (b) (4) may lead to confusion and medication errors. Furthermore, (b) (4) information should not compete in size and prominence with critical information on the principal display panel.	Where presented, we recommend relocating the (b) (4) logo “ORGANON” (b) (4) See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
3.	As currently presented, the storage information	The storage information should align with the PI.	Revise the storage information to read “Store refrigerated at

Table 3. Identified Issues and Recommendations for Shanghai Henlius Biotech, Inc.
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	does not align with the Prescribing Information (PI). Additionally, the temperature numerical value is missing the degree symbol and the storage information lack prominence.	Additionally, lack of clarity and prominence may result in important storage information being overlooked.	2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Bildyos must not be exposed to temperatures above 25°C/77°F. Do not freeze. Avoid excessive shaking. Once removed from the refrigerator, Bildyos must be used within 30 days. Discard Bildyos if not used within the 30 days. Do not use Bildyos after the expiry date printed on the label. "
4.	The principal Display Panel (PDP) does not include the statement that Bildyos should be administered by a healthcare provider.	Failure to include instructions on the carton labeling may result in patients or caregivers administering the product, which may lead to medication errors. The statement will help alert patients, caregivers, and healthcare providers (particularly pharmacies who may dispense the product directly to the patient) that the patient should take the product to their healthcare provider for administration.	On the PDP add the statement "Bildyos should be administered by a healthcare provider."
5.	As currently presented, there is (b) (4) on the carton.	This drug is (b) (4)	We recommend deleting the following (b) (4)
Prefilled Syringe Carton Labeling			

Table 3. Identified Issues and Recommendations for Shanghai Henlius Biotech, Inc.
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The Medication Guide (MG) statement is located (b) (4)	Ensure the Medication Guide statement appears in accordance with 21 CFR 208.24(d). Additionally, the statement (b) (4) appears disconnected from the MG statement and may be confusing in its intended meaning.	Relocate the MG statement to the Principal Display Panel (PDP) and ensure it appears on the label in a prominent and conspicuous manner. Additionally, combine the statement (b) (4) with the MG statement (b) (4) to assure a cohesive message.
2.	As currently presented, (b) (4) and it overcrowds the information it is adjacent to (b) (4)	Information overcrowding may lead to readability issues and medication errors.	Consider removing (b) (4) or create sufficient white space between each statement to improve readability without decreasing font size of other critical information.
3.	As currently presented, the proprietary name and proper name lack prominence on the principal display panel as the strength appears more prominent in size.	The proprietary name and proper should be the most prominent information on the principal display panel (PDP).	We recommend increasing the prominence of the proprietary name and established name. Consider the use of different font type or size, bolding, color, or other means to achieve increased prominence and decreasing the font size of the strength on the PDP. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
Vial Carton Labeling			

Table 3. Identified Issues and Recommendations for Shanghai Henlius Biotech, Inc.
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The “Rx only” statement appears more prominent than other critical information (e.g., route of administration) on the principal display panel (PDP).	The “Rx only” statement should not compete in size and prominence with critical information on the principal display panel.	We recommend the “Rx only” statement does not compete in size or prominence with critical information on the principal display panel. Consider decreasing the font size and relocating it to the bottom of the PDP. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
2.	A Medication Guide (MG) statement is missing from the principal display panel (PDP) of the carton labeling.	Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner.	Ensure the Medication Guide statement appears in accordance with 21 CFR 208.24(d) on the PDP.
3.	On the side panel the net quantity statement “One 1 mL Single-dose Vial...” (b) (4)	Minimize the risk for numerical confusion.	On the side panel, ensure that the net quantity statement is located (b) (4) You may consider deleting the net quantity statement from the side panels

Table 3. Identified Issues and Recommendations for Shanghai Henlius Biotech, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			or relocating it to the bottom corner of the display.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Bıldıys received on March 14, 2025, from Shanghai Henlius Biotech, Inc.

Table 4. Relevant Product Information for Bıldıys and Prolia		
Product Name	Bıldıys	Prolia ^a (BLA 125320)
Initial Approval Date	N/A	June 1, 2010
Nonproprietary Name	denosumab- nxxp	denosumab
Indication	Treatment of postmenopausal women with osteoporosis at high risk for fracture. Treatment to increase bone mass in men with osteoporosis at high risk for fracture. Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture. Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.	
Dosage Form	injection	
Strength	60 mg/mL	
Route of Administration	subcutaneous	
Dose and Frequency	60 mg subcutaneous injection once every 6 months	
How Supplied	60 mg/mL in a single-dose prefilled syringe. 60mg/mL in a single-dose vial.	60 mg/mL single-dose prefilled syringe.

^a Prolia [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125320s0000lbl.pdf

Table 4. Relevant Product Information for Bildyos and Prolia		
Product Name	Bildyos	Prolia ^a (BLA 125320)
Storage	Store (b) (4) at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Prior to administration, may be allowed to reach room temperature (up to 25°C/77°F) in the original container. Once removed from the refrigerator, must not be exposed to temperatures above 25°C/77°F and must be used within 30 days. If not used within the 30 days should be discarded. Do not use after the expiry date printed on the label. Protect from direct light and heat. Avoid vigorous shaking.	Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, do not expose the product to temperatures above 25°C (77°F) and use the product within 14 days. If not used within 14 days discard the product. Protect from direct light and heat and avoid vigorous shaking.
Container Closure	single-dose prefilled syringe single-dose vial	single-dose prefilled syringe

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,^b along with postmarket medication error data, we reviewed the following Bildyos labels and labeling submitted by Shanghai Henlius Biotech, Inc.

- Prescribing Information and Medication Guide (MG) received on March 14, 2025, available from <\\CDSESUB1\EVSPROD\bla761444\0015\m1\us\114-labeling\draft\labeling\drafted-uspi-bildyos.pdf>
- Container labels received on April 14, 2025
- Carton labeling received on April 14, 2025

B.2 Container Labels and Carton Labeling Images

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Container Labels:



(b) (4)

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 27, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761444
Product Name, Dosage Form, and Strength:	Bilprevda (denosumab-nxxp) injection, 120 mg/1.7 mL (70 mg/mL)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Shanghai Henlius Biotech, Inc. (Henlius)
FDA Received Date:	March 14, 2025, and April 14, 2025
TTT ID #:	2024-10712
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 INTRODUCTION

As part of the approval process for Bilprevda (denosumab-nxxp) injection, the Division of General Endocrinology (DGE) requested that we review the proposed Bilprevda Prescribing Information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Bilprevda (denosumab-nxxp) is a proposed 351(k)(4) interchangeable and the US-licensed Reference Product (RP) is Xgeva (denosumab), BLA 125320.

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

3 CONCLUSION

The proposed Bilprevda Prescribing Information (PI), container label, 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 Endocrinology (DGE) in Section 4 and for Shanghai Henlius Biotech, Inc. in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

Table 2. Identified Issues and Recommendations for the Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	We note a conditionally acceptable nonproprietary name suffix has been approved on May 29, 2025.	Revise the nonproprietary name on all labeling to incorporate the FDA-designated nonproprietary name suffix, “-nxxp”, appended to the core name, “denosumab”, so that the proper name appears as “denosumab-	Replace the suffix placeholder “-xxxx” with the approved suffix “nxxp”.

Table 2. Identified Issues and Recommendations for the Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		nxxp” throughout the labeling. See Draft Guidance for Industry: Nonproprietary Naming of Biological Products: Update (March 2019).	
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The product strength is 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) for consistency.	Add the strength in accordance with 21 CFR 201.57 (c) (17). Revise the strength description to read “120 mg/1.7 mL (70 mg/mL)”.

5 RECOMMENDATIONS FOR SHANGHAI HENLIUS BIOTECH, INC.

Table 3. Identified Issues and Recommendations for Shanghai Henlius Biotech, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	As currently presented the small size of the container label renders the critical information (e.g., proprietary name, proper name, strength, etc.) on the label difficult to read.	Per 21 CFR 201.10(i), the small label is required to have the following minimum amount of information: proprietary name, established name, product strength, Identifying lot or control number, name of manufacturer, packer, or distributor, expiration date, and barcode (per 21CFR 201.25(c)(2)).	We recommend increasing the readability of the proprietary name, proper name, and strength by increasing the font size. You may consider removing not minimally required information (e.g., Single-dose Vial. Discard unused portion, etc.) on the container label.
2.	We note a conditionally acceptable nonproprietary name suffix has been approved on May 29, 2025.	Should your BLA be approved during this review cycle, “denosumab- nxxp” will be the proper name designated in the license. Revise the nonproprietary name on all labeling to incorporate the FDA-designated nonproprietary name suffix, “-nxxp”, appended to the core name, “denosumab”, so that the proper name appears as “denosumab-nxxp” throughout the labeling. See Draft Guidance for Industry: Nonproprietary Naming of Biological Products: Update (March 2019).	Replace the suffix placeholder “-xxxx” with the approved suffix “nxxp”.

Table 3. Identified Issues and Recommendations for Shanghai Henlius Biotech, Inc.
(entire table to be conveyed to Applicant)

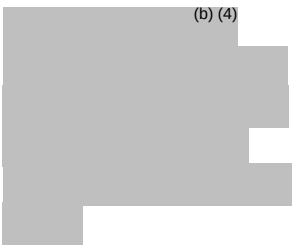
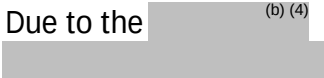
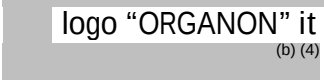
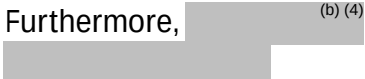
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
1.	We note a conditionally acceptable nonproprietary name suffix has been approved on May 29, 2025.	Should your BLA be approved during this review cycle, “denosumab- nxxp” will be the proper name designated in the license. Revise the nonproprietary name on all labeling to incorporate the FDA-designated nonproprietary name suffix, “-nxxp”, appended to the core name, “denosumab”, so that the proper name appears as “denosumab-nxxp” throughout the labeling. See Draft Guidance for Industry: Nonproprietary Naming of Biological Products: Update (March 2019).	Replace the suffix placeholder “-xxxx” with the approved suffix “nxxp”.
2.	The manufactured-for name and logo “ORGANON” is located  (b) (4)	Due to the  (b) (4) logo “ORGANON” it  (b) (4) may lead to confusion and medication errors. Furthermore,  (b) (4) information should not compete in size and prominence with critical information on the principal display panel.	We recommend relocating the  (b) (4) logo “ORGANON”  (b) (4) such as to the visual space containing storage information.
3.	As currently presented, the storage information	The storage information should align with the PI.	Revise the storage information to read “Store refrigerated at

Table 3. Identified Issues and Recommendations for Shanghai Henlius Biotech, Inc.
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	does not align with the Prescribing Information (PI). Additionally, the temperature numerical value is missing the degree symbol, and the storage information lacks prominence.	Additionally, lack of clarity and prominence may result in important storage information being overlooked.	2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Avoid excessive shaking. Prior to administration, Bilprevda may be allowed to reach room temperature up to 25°C (77°F) in the original container. Once removed from the refrigerator, Bilprevda must not be exposed to temperatures above 25°C (77°F) and must be used within 30 days. Discard TRADENAME if not used within the 30 days. Do not use Bilprevda after the expiry date printed on the label."
4.	The principal Display Panel (PDP) does not include the statement that Bilprevda should be administered by a healthcare provider.	Failure to include instructions on the carton labeling may result in patients or caregivers administering the product, which may lead to medication errors. The statement will help alert patients, caregivers, and healthcare providers (particularly pharmacies who may dispense the product directly to the patient) that the patient should take the product to their healthcare provider for administration.	On the PDP add the statement "Bilprevda should be administered by a healthcare provider."
5.	On the side panel the net quantity statement "One 1.7 mL Single-dose	Minimize the risk for numerical confusion.	On the side panel, ensure that the net quantity statement is located (b) (4)

Table 3. Identified Issues and Recommendations for Shanghai Henlius Biotech, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Vial... (b) (4)		(b) (4) You may consider deleting the net quantity statement from the side panels or relocating it to the bottom corner of the display.
6.	As currently presented, there is (b) (4) on the carton.	This drug is (b) (4)	We recommend deleting the following, (b) (4)
7.	The “Rx only” statement appears more prominent than other critical information (e.g., route of administration) on the principal display panel (PDP).	The “Rx only” statement should not compete in size and prominence with critical information on the principal display panel.	We recommend the “Rx only” statement does not compete in size or prominence with critical information on the principal display panel. Consider decreasing the font size and relocating it to the bottom of the PDP. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Bilprevda received on March 14, 2025, from Shanghai Henlius Biotech, Inc.

Table 4. Relevant Product Information for Bilprevda and Xgeva		
Product Name	Bilprevda	Xgeva ^a (BLA 125320)
Initial Approval Date	N/A	June 1, 2010
Nonproprietary Name	denosumab-nxxp	denosumab
Indication	• Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. • Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.	
Dosage Form	injection	
Strength	120 mg/1.7 mL (70 mg/mL)	
Route of Administration	subcutaneous	
Dose and Frequency	Multiple myeloma and bone metastasis from solid tumors: • 120 mg every 4 weeks Giant cell tumor of bone: • 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy Hypercalcemia of malignancy: • 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy	
How Supplied	120 mg/1.7 mL in a single-dose vial (1 vial per carton)	

^a Xgeva [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Jun 2020. [cited 2025 May 20]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125320s203lbl.pdf.

Table 4. Relevant Product Information for Bilprevda and Xgeva		
Product Name	Bilprevda	Xgeva ^a (BLA 125320)
Storage	Store (b) (4) at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, (b) (4) must not be exposed to temperatures above 25°C/77°F (b) (4) and must be used within 30 days. Discard if not used within the 30 days. Do not use after the expiry date printed on the label. Protect from direct light and heat. Avoid vigorous shaking.	Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, product must not be exposed to temperatures above 25°C/77°F or direct light and must be used within 14 days. Discard if not used within the 14 days. Do not use after the expiry date printed on the label. Protect from direct light and heat. Avoid vigorous shaking.
Container Closure	Single-dose vial	

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,^b along with postmarket medication error data, we reviewed the following Bilprevda labels and labeling submitted by Shanghai Henlius Biotech, Inc.

- Prescribing Information received on March 14, 2025, available from \\CDSESUB1\EVSPROD\bla761444\0015\m1\us\114-labeling\draft\labeling\drafted-uspi-bilprevda.pdf
- Container label received on April 14, 2025
- Carton labeling received on April 14, 2025

B.2 Container Label and Carton Labeling Images

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Container Label:



(b) (4)

Carton Labeling:



(b) (4)

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/s/

PEGGY M RAHBANI
06/30/2025 07:07:47 AM

YEVGENIYA M KOGAN
06/30/2025 08:37:04 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 26, 2025

TO: Dr. Theresa Kehoe, MD
Director
Division of General Endocrinology (DGE)
Office of Cardiology, Hematology, Endocrinology and
Nephrology (OCHEN)
Office of New Drug (OND)

FROM: Yi-Ying Chen, MSc., MSRA
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Dr. Arindam Dasgupta, Ph.D.
Director
DNDSI
OSIS

SUBJECT: Review of Analytical Inspection of (b) (4)
(b) (4)

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical inspection of Study HLX14-001 (Part II), submitted under BLA 761444, [HLX14 (denosumab), a proposed biosimilar to Prolias, injection solution] conducted at (b) (4)
(b) (4)

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. Based on the inspection findings, there are no identified concerns for (b) (4)
(b) (4) regarding reliability of the data for inspected study HLX14-001 (Part II) for the review division consideration.

2. Inspected Studies:

BLA 761444

Study Number: HLX14-001 (Part 2, including 228 subjects for PK, ADA and NAb)

Study Title: "A Randomized, Parallel, Single-dose, Subcutaneous Injection, Phase I Clinical Study of

HLX14 versus Prolia® (Denosumab) in Chinese Healthy Adult Male Subjects for Comparison in Pharmacokinetic Characteristics, Safety, and Immunogenicity"

Dates of Study Conduct: 01/03/2023 - 09/27/2023 (PK analysis)
08/22/2023 - 11/14/2023 (ADA and NAb)

Analytical Site:

(b) (4)

(b) (4)

3. Inspectional Findings

(b) (4)

I, OSIS scientist Yi-Ying Chen, MSc. inspected

(b) (4)

(b) (4)

3.1 Previous Inspection

This was the first OSIS inspection of
(b) (4) under the BA/BE program.

(b) (4)

3.2 Current Inspection

The current inspection included auditing the following items:

- Source records of method validation
- Source records of study sample analysis
- Standard operating procedures (SOPs)
- Sample receipt and storage
- Facility for bioanalytical operations
- Calibration and maintenance records
- Audit trails of project and instruments (SpectraMax and Meso Scale Discovery) used in the reviewed studies
- Interviews with the firm's management and staff

3.3 Inspection finding

At the conclusion of the inspection, I did not observe any objectionable conditions and did not issue Form FDA 483 to the analytical site.

(b) (4)

Yi-Ying Chen, MSc., MSRA
Chemist

Draft: YEC 06/15/2025, 06/16/2025

Edit: GB 06/16/2025, 06/26/2025

OSIS File #:

(b) (4)

eNSpect Assignment ID:

(b) (4)

eNSpect OpID:

(b) (4)

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/s/

YIYING E CHEN
06/26/2025 06:25:32 PM

GOPA BISWAS
06/27/2025 09:30:55 AM

Clinical Inspection Summary

Date	May 16, 2025
From	Ling Yang, M.D., Ph.D., FAAFP 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	Milalynn Victorino, M.D., Clinical Reviewer Thomas Herndon, M.D., Clinical Team Leader Alice Lee, Pharmacist, RPM Division of General Endocrinology (DGE)
BLA #	761444
Applicant	Shanghai Henlius Biotech, Inc.
Drug	BILPREVA (HLX14; denosumab-xxxx); proposed biosimilar to Prolia®
NME (Yes/No)	No
Review Priority	Standard
Proposed Indication(s)	Treatment of postmenopausal women with osteoporosis at high risk for fracture
Consultation Request Date	October 10, 2024
Summary Goal Date	June 04, 2025
Action Goal Date	July 04, 2025
PDUFA Date	July 04, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study **HLX14-002-PMOP301** entitled “Randomized, Double-blind, International Multicenter, Parallel-controlled Phase III Clinical Study to Evaluate Recombinant Anti-RANKL Human Monoclonal Antibody Injection (HLX14) versus Denosumab Injection (Prolia®) in Postmenopausal Women with Osteoporosis at High Risk of Fracture” were submitted in this original Biological License Application (BLA) for BILPREDA (HLX14; denosumab-xxxx) that is proposed biosimilar to Prolia® for treatment of postmenopausal women with osteoporosis at high risk for fracture. Two foreign (China) clinical investigators (CIs): Drs. Qun Xia (Site #11115) and Ping Jin (Site #11130) were inspected for the submitted study. In addition, the contract research organization (CRO) (b) (4) who conducted central image reading for the primary endpoint data, was also inspected.

Based on the overall inspection results of these CIs and the CRO, and the regulatory assessments, the data generated by the CIs and the CRO are verifiable. Study HLX14-002-PMOP301 appears to have been conducted adequately and the clinical data submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Prolia® (denosumab) 60 mg/mL subcutaneous (SC) injection was approved on 06/01/2010 under BLA 125320 for treatment of postmenopausal women with osteoporosis at high risk for fracture. Shanghai Henlius Biotech, Inc. (Henlius) submitted an original BLA 761444 on 08/30/2024 for HLX14 (denosumab-xxxx), proposed biosimilar to Prolia®. The proposed name is BILPREVDA. Data from a Phase 3 study HLX14-002-PMOP301 were submitted to support the approval.

Study HLX14-002-PMOP301

Study HLX14-002-PMOP301 was a randomized, double-blind, multicenter, parallel-controlled Phase 3 study to evaluate HLX14 versus Prolia® in postmenopausal women with osteoporosis at high risk of fracture.

The primary study objectives were to assess the primary clinical efficacy endpoint and pharmacodynamic (PD) endpoint between HLX14 and Prolia® in postmenopausal women with osteoporosis at high risk of fracture.

The primary efficacy endpoints were the percent change from baseline in bone mineral density (BMD) calculated as: $(\text{test value} - \text{baseline value}) / (\text{baseline value}) \times 100\%$ at the lumbar spine (LS) to Week 52 (assessed by the central imaging); and the area under the effect-time curve for percent change of serum type I collagen C-telopeptide (s-CTX) from baseline to Week 26 (AUEC0-26W).

Study Design:

The study consisted of the following periods:

- **Screening Period:** up to 4 weeks
- **Treatment Period I:** 52 weeks. Eligible subjects were randomized in a 1:1 ratio to receive 2 doses of HLX14 or Prolia. The first dose was administered following randomization. The second dose was administered 26 weeks after the first dose.
- **Treatment Period II:** 26 weeks. At Week 52, subjects in the Prolia arm were re-randomized in a 1:1 ratio to either continue with a third dose of Prolia or transition to HLX14 to receive a single dose of HLX14 to assess immunogenicity and safety after a transition from Prolia to HLX14. Subjects in the HLX14 arm received a 3rd dose of HLX14.

The study screened 1078 subjects, randomized 514 (256 in HLX14 group and 258 in Prolia group) subjects at 40 study sites in 2 countries: China (38) and Australia (2). The first subject was randomized on 06/17/2022 and the last subject's last visit was on 06/05/2024. A total of 478 (236 in HLX14 group and 242 in Prolia group) subjects completed the 52-week treatment period. A total of 220 subjects from Prolia group were randomized for Treatment Period 2 (110 in HLX14 group, and 110 in Prolia group). A total of 435 subjects (219 in HLX14/HLX14 group, 108 in Prolia/Prolia group, and 108 in Prolia/HLX14 group) completed the 76-week Treatment Period. The database was locked on 07/03/2024.

III. RESULTS

1. Qun Xia, M.D. (Site #11115)

No. 24 Fukang Road, Nankai District
Tianjing, 300074
China

This CI was inspected on 02/17-20/2025 as a data audit for Study HLX14-002-PMOP301. This was the first FDA inspection of Dr. Xia. The inspection was facilitated by an independent interpreter.

For the inspected study, the site screened 65 subjects and enrolled 30 subjects. Twenty-five (25) subjects completed the study. The first subject consented on (b) (6) and the last subject's last visit was on (b) (6). Source records for 15/30 enrolled subjects were reviewed.

The inspection reviewed the study protocols and amendments, Informed Consent Forms (ICFs) and versions, documentation of eligibility criteria and enrollment logs, medical records [including visit data, laboratory tests, physical exam results, adverse events (AEs) and serious AEs (SAEs) reports], investigational product (IP) accountability records, both paper and electronic Case Report Forms (eCRFs) and electronic data capture (EDC) system, protocol deviations and related regulatory documents [e.g., Ethics Committee (EC) approvals and communications, staff trainings, monitoring log, records retention, financial disclosures and delegation of authority].

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data of the percent change from baseline in LS-BMD scores by DXA scans at Week 52 were centrally assessed. Source records for the BMD scores received from the sponsor were verified with the submitted data listing with no discrepancies identified. There were no underreporting of AEs or SAEs.

The inspection noted that four subjects [(b) (6) (HLX14/not treated), (b) (6) (HLX14/not treated), (b) (6) (HLX14/not treated) and (b) (6) (HLX14/not treated)] discontinued the study treatment but continued the study without signing the ICF V5.0. All 4 subjects continued study-related procedures until Week 52, although they refused to receive the 2nd dose at Week 26.

The additional items were discussed at the end of the inspection including:

- The blinding status of the clinical pharmacist, clinical research coordinator and the DXA technician were not specified.
- Subject # (b) (6) (HLX14/HLX14 group) received the incorrect IP kit (4635 instead of 4365) on (b) (6) at Week 26. The subject was contacted on (b) (6) and reported no AEs.

Reviewer's Comments:

- *In the submission, the status of the four subjects who did not receive the 2nd dose of the IP were reported as "discontinued". Although the ICF Version 5.0 should be obtained in those four subjects, this has no significant impact on the study results.*

- The CI responded on (b) (6) that all 4 subjects signed the ICF V4.0, which provided valid consent. Actions are implemented to improve the quality of future study. The CI's response is acceptable.
- Subject # (b) (6)'s use of incorrect kit was submitted as a protocol deviation that raised no concerns. The incorrectly used IP kit 4635 belonged to Subject # (b) (6) (HLX14/HLX14 group), who also would receive HLX14. Thus, Subject # (b) (6) received the same (HLX14) treatment even the IP kit was not correct.

In general, the inspection verified adequate source data for the inspected studies subjects, with no deficiencies reported.

2. Ping Jin, M.D., Ph.D. (Site #11130)

138 Tongzipo Road
Yuelu, Changsha
Hunan, 410013
China

This CI was inspected on 02/24-28/2025 as a data audit for Study HLX14-002-PMOP301. This was the first FDA inspection of Dr. Jin. The inspection was facilitated by an interpreter assigned by the US State Department.

For the inspected study, the site screened 46 subjects and enrolled 28 subjects. The first subject consented on (b) (6) and the last subject's last visit was on (b) (6). Source records for 15/28 enrolled subjects and 10/18 screen failure subjects were reviewed.

The inspection reviewed the study protocols and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit data, laboratory tests, AEs and SAEs reports), IP accountability records, paper CRFs with eCRFs entries and audit trails, EDC system, protocol deviations and related regulatory documents (e.g., EC approvals and communications, staff trainings, monitoring procedure and logs, records retention, financial disclosures and delegation of authority).

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data of the percent change from baseline in LS-BMD scores by DXA scans at week 52 were centrally assessed. Source records for the BMD scores received from the sponsor were verified with that of submitted data listing with no discrepancies identified. There were no underreporting of AEs or SAEs.

In general, the inspection verified adequate source data for the inspected studies subjects, with no significant deficiencies noted.

3. (b) (4) (CRO)



The CRO (b) (4) was inspected on (b) (4) as a data audit for Study HLX14-002-PMOP301. The company (b) (4) was renamed (b) (4). This was the first FDA inspection of the CRO (b) (4).

The focus of the inspection was the CRO's responsibilities and activities as a central imaging DXA scan BMD score reader. The inspection also reviewed the CRO's organizational charts; the study protocol; procedures related to the data management and review process; DXA scan data collection, central reading, and storage procedures; data verification; quality control and computer softwares and system validation procedures.

The inspection reviewed source data of DXA scan results of the adjusted BMD (g/cm²) and T-score values at baseline, Week 26, and Week 52 for subjects at sites #11115 and #11130.

The inspection found that the CRO used the computerized systems (Hologic Apex and Lunar enCORE) to analyze DXA images acquired at the CI sites. These computerized systems are not 21CFR Part 11 compliant.

The inspection also noted the following 2 quality events that were identified by the sponsor/CRO during the study:

Event (b) (4) -06296:

- Correction factors were improperly applied during the final data transfer (06/26/2024) to the sponsor, affecting BMD data for 31 subjects (3.5% of study population).
- The sponsor discovered the discrepancies between data received from the interim transfer on 01/12/2024 and that of "final" transfer on 06/26/2024. Data were corrected by the CRO on 07/13/2024.
- The CRO found that the root cause was prior QC corrections were overwritten instead of appended according to standard procedure.

Event (b) (4) -06317:

- Hip data for three subjects (# (b) (6)) were improperly excluded from the data transfer file on 12/28/2023. The CRO found the problem on 07/18/2024 and corrected the data.
- The root cause was scanning data in DXAsure was not updated to match data in QUMAS (Document Management Platform) system.

Reviewers' Comments:

- *The CRO responded on 03/19/2025 that the two software systems (Hologic Apex and Lunar enCORE) used for DXA scan analysis are FDA approved. They are Commercial-Off-The-Shelf (COTS) and commercially available. DXA scan results read by the software were saved as PDF files with a date and time stamp and were checked into the validated DXAsure and Document Management Platform (QUMAS) systems (used for DXA scan data receiving, processing and storage of final reading results) that has audit trails and can mitigate risks of Part 11 gap. Any edits/modifications and deletion made in the software were detectable and*

fully auditable from the DXA sure and QUMAS systems. In addition, the systems' QC checks ensured that the DXA analysis data in the software match 100% with those in the DXA sure and QUMAS. The CRO's responses to the inspection findings are deemed acceptable.

- Events (b) (4)-06296 and (b) (4)-06317 were identified and corrected by the sponsor and the CRO before data submission. Thus, these events should not have any effects on the data reliability and analysis.
- The inspection findings were discussed with the review division on 05/01/2025 and the division expressed no concerns on the data quality and reliability.

In general, the CRO's management of Study HLX14-002-PMOP301 and central reading of the DXA scan for BMD scores appear adequate, with no significant deficiencies noted.

Additional Information Verified by OSI

- An Information Request (IR) was sent to the sponsor on 04/21/2025 and 04/28/2025 requesting certified copies of individual subjects' s-CTX results (co-primary endpoint) assessed at central lab for Sites #11115 and #11130. The IR response was received on 05/01/2025.
- The reviewer compared the original lab copies of s-CTX levels at baseline and Week 26 with the submitted data listing in randomly selected 10 of 30 enrolled subjects (b) (6)

(b) (6)
at Site #11130. No discrepancies were identified.

{See appended electronic signature page}

Ling Yang, 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
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Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Director, Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.\BLA 761444
DGE\CDTL\Thomas Herndon
DGE\Reviewer\Milalynn Victorino
DGE\Project Manager\Alice Lee
OSI\Director\David Burrow
OSI\Deputy Director\Laurie Muldowney
OSI\DCCE\Division Director\Kassa Ayalew
OSI\DCCE\GCPAB\Branch Chief\Jenn Sellers
OSI\DCCE\GCPAB\Team Leader\Min Lu
OSI\DCCE\GCPAB\Reviewer\Ling Yang
OSI\DCCE\Program Analysts\Yolanda Patague

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/s/

LING YANG
05/16/2025 11:41:56 AM

MIN LU
05/16/2025 11:47:36 AM

JENN W SELLERS
05/16/2025 11:50:49 AM

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	4/21/2025
To:	Kristine Leahy
Requesting Center/Office	CDER/OPQ
From	Cassandra O'Donnell OPEQ/OHT3/DHT3C
Through (Team)	Rong Guo, Acting Team Lead, Injection Devices OPEQ/OHT3/DHT3C
Through (Division) *Optional	Shruti Mistry, Assistant Director, Injection Devices OPEQ/OHT3/DHT3C
Subject	ICCR: ICCR01023443 ICC: ICC2400938 Submission: BLA761444 Sponsor: Shanghai Henlius Biotech, Inc. Drug/Biologic: HLX-14 (Denosumab) Indications for Use: 1. Treatment of postmenopausal women with osteoporosis at high risk for fracture. 2. Treatment to increase bone mass in men with osteoporosis at high risk for fracture. 3. Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture. 4. Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. 5. Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. 6. Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. 7. Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.
Recommendation	Final Recommendation: ☒ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, ☐ Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies Comments to Review Team: CDRH would like to recommend in future marketing applications that the sponsor provide sample sizes for needle safety device essential performance requirements that support a confidence and reliability of 95%/99% for each condition (e.g. simulated shipping, accelerated aging, drop, etc.) PMC/PMR or CR Deficiencies: N/A

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (*Optional)
CASSANDRA K. O'DONNELL -S 2025.04.21 09:50:18 -07'00'	Shruti N. Mistry -S	2025.04.21 14:21:34 -04'00'

1. PURPOSE

This review provides an assessment of the needle safety device constituent part¹ of the prefilled syringe product.

This review will cover the following review areas:

☒ Needle safety device constituent performance ¹

CDRH Quality Systems Assessment / Facilities consult not required per internal MAP 5017.7

It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential²) treatment that are administered by non-health care professionals.

2. DEVICE DESCRIPTION

3.2.P.7 Container Closure System (HLX14, 60mg/PFS)

HLX14 (60 mg, PFS) is a single dose combination product. The finished device presentation includes a PFS accessorized with a passive needle safety device and plunger rod. The illustration of HLX14 (60 mg, PFS) combination product is shown in [Figure 3.2.P.7.1](#).



¹ The scope of this review will be limited to the device constituent performance in accordance with ISO 23908:2011 Sharps Injury Protection and FDA guidance Medical Devices with Sharps Injury Prevention Features. Therefore, for a PFS with a needle safety device constituent the review will be limited to needle safety performance requirements and will not cover functions of the primary container (container content, breakloose force, glide force, needle shield removal force, etc.,).

² Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

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The container closure system is a 1 mL long (b) (4) syringe with a 29G 1/2-5B needle (Cat#: (b) (4)) and a (b) (4) rubber plunger stopper (Cat#: (b) (4)) or (b) (4) rubber plunger stopper (Cat#: (b) (4)). The components of the (b) (4) syringes include a (b) (4) glass syringe barrel, a hypodermic stainless-steel needle, an elastomeric needle shield and a (b) (4) rigid shield. The rubber plunger stoppers of both suppliers are made of elastomer (formulation: (b) (4)). All components are not made with natural rubber latex or dry natural rubber. The PFS is accessorized with a passive needle guard (BD UltraSafe PLUS™ (b) (4)) (Cat#: (b) (4)) and a plunger rod (BD UltraSafe PLUS™ (b) (4)) (Cat#: (b) (4)). Details of HLX14 (60mg PFS) primary Packaging is provided in Table 3.2.P.7.1. The drawings of the device components are provided in Appendix 1 to Appendix 4.

Step	Schematic figure
	(b) (4)

Appendix 3 Drawing of Safety Passive Needle Guard

(b) (4)

Table 6 Key Functional Elements of HLX14 (60 mg, PFS) combination product

Part	Component	Material	Contact With the Human Body
Glass Syringe with Rigid Needle Shield	Syringe barrel	(b) (4) glass	Intact skin
	Hypodermic needle	Stainless steel	Direct
	Rigid Needle Shield (RNS) made of rigid shield (RS) plus needle-shield (NS)	Elastomer (NS) (b) (4) (RS)	Blood path, indirect
Stopper	Stopper	Elastomeric (formulation: (b) (4))	Indirect
Plunger Rod	Plunger Rod		Intact skin
Needle Safety Device	Guard		Intact skin
	Body		Intact skin
	Spring	Stainless Steel	Indirect

2.3 Recommended Dosage

Bildyos should be administered by a healthcare professional.

The recommended dose of Bildyos is 60 mg administered as a single subcutaneous injection once every 6 months. Administer Bildyos via subcutaneous injection in the upper arm, the upper thigh, or the abdomen. All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily [see *Warnings and Precautions* (5.1)].

If a dose of Bildyos is missed, administer the injection as soon as the patient is available. Thereafter, schedule injections every 6 months from the date of the last injection.

(b) (4)

Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Professional Use and Self-Administration
Needle connection (e.g. luer, slip tip, staked)	Staked
Needle safety type (active or passive)	Passive Needle Guard

3. FILING REVIEW

Checklist	Present		
Item	Yes	No	N/A
Device Description	X		
Letters of Authorization	LOA provided for		

	DMF# 037027		
Design Verification Summary and reports for needle safety attributes	Provided in response to IRs# 1.1-1.3		

4. DEVICE PERFORMANCE REVIEW

4.1. Performance Data

Performance Requirement	Specification	Confidence / Reliability	Verification Data Acceptable (Y/N)
Needle Safety Activation force	(b) (4)	(b) (4)	Acceptable N=30 per lot; n=60 per timepoint Lot #1: 9.3±1.9N Lot #2: 9.7±1.4N 95/97.5%; variable; K _{expected} : 2.608 Sponsor pooled results from all conditions for a sample size of n=720 and 95%/99%.
Needle safety override force			Acceptable N=60 per lot; n= 120 per timepoint 95% / 95%, Attribute Sponsor pooled results from all conditions for a sample size of n=870 and 95%/99%.
Needle Safety Pre-activation			N=30 per batch; n=60 total 95/97.5%, Attribute
Needle safety Access in safe mode			Sphere test Method Described in ISO 23908 Annex B. Sponsor is leveraging BD Sphere test method data

Table 3 List of Design Verification Function Tests

Test condition	Test method category	PF	Initial risk	Acceptable criteria	Confidence/reliability	Sample size ^[1]	k-expected
Long term aging (2-8°C), accelerated aging (25°C±2°C/60%±5% RH) simulated transport, free-fall ^[3]	Variable	Deliverable volume	Medium	(b) (4)		N=30	2.921
		Cap removal force	Medium			N=60	2.67
		Break Loose Force	Medium			N=30	2.608
		Glide Force	Medium			N=30	2.608
		Safety activation force (Pre-activation ^[4])	Medium			N=30	2.608
	Attribute	CCI	Medium			N=60	N/A ^[2]
		Override Force	Medium			N=60	N/A ^[2]
Note:							
(b) (4)							

Batch		E2308004	2309091	E2404001
	Needle Safety Device	Manufacturer: Becton Dickinson Cat No: 47451130		
Test Plan	Long term aging (2-8°C)	X (up to 12 M)	-	X (up to 6 M)
	Accelerated aging (25°C±2°C/60%±5% RH)	X (up to 9 M)	-	X (up to 6 M)
	Simulated shipping	X	-	-
	Free fall	-	X	-

Table 5 Design verification plan for HLX14 (60 mg, PFS) combination product

Test item	Long term aging (2-8°C) Month									Accelerated aging (25°C±2°C) Month				Simulated shipping [1]	Free fall [2]
	0	1	3	6	9	12	18	24	36	1	3	6	9		
Needle Shield Removal Force	X	X	-	X	-	-	X	X	X	X	-	X	X	X	X
Break Loose Force	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Glide Force	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Activation Force (Pre- activation ^[3])	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Override Force	X	X	-	X	-	-	-	-	X	X	-	X	X	X	X
Deliverable volume	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI ^[4]	X	X	-	X	-	-	-	-	X	X	-	X	X	X	-
Note:															
(b) (4)															
[5] X = yes, - = no															

Table 1 Test results under long-term aging condition (2-8°C)

Test item	Acceptable criteria	Confidence/r eliability	Lot#	Sample Size per timepoint	Statistical parameter	T0	Long term aging (2-8°C)					
							Month					
							1	3	6	9	12	
Needle safety activation force	(b) (4)		E2308004	N=30	Mean	(b) (4)						
					SD	1.9	2.6	1.5	2.1	1.7	1.4	
					Min	7.6	7.8	7.8	7	7.6	7.6	
					Max	15.4	15.7	14	14.7	14.6	14	
					k-expected	2.608						
					k-actual	8.162	5.665	10.223	7.361	9.681	11.449	
			E2404001	N=30	Mean	(b) (4)						
					SD	1.4	1.5	1.6	1.5	1.5	TBD	
					Min	7.1	7.9	7.5	8.1	7.3	TBD	
					Max	12.4	12.9	13.3	14	12.7	TBD	
					k-expected	2.608						
					k-actual	10.923	10.176	8.911	10.086	10.321	TBD	
Needle safety override force				E2308004	N=60	N/A ^[1]	Pass	Pass	- ^[2]	Pass	-	-
				E2404001	N=60	N/A	Pass	Pass	-	Pass	-	-

[1]: N/A represents "Not Applicable".

[2]: - represents that no sampling is conducted at this timepoint.

[3]: TBD represents that the results are pending update, so it is marked as "To Be Determined".

Table 3 Test results under simulated shipping condition

Test item	Acceptable criteria	Confidence/reliability	Lot#	Sample Size per timepoint	Statistical parameter	Simulated shipping
Needle safety activation	(b) (4)		E2308004	N=30	Mean	(b) (4)
					SD	2.2
					Min	6.4
					Max	15.6
					k-expected	2.608
			k-actual	6.849		
Needle safety override force			E2308004	N=60	N/A ⁽¹⁾	Pass

⁽¹⁾: N/A represents "Not Applicable".

Table 4 Test results under free fall condition

Test item	Acceptable criteria	Confidence/reliability	Lot#	Sample Size per timepoint	Statistical parameter	Free fall	
Needle safety activation	(b) (4)	2309091	N=30	Mean	(b) (4)		
				SD	2.2		
				Min	7.3		
				Max	16.2		
				k-expected	2.608		
Needle safety override force			2309091	N=60	N/A ⁽¹⁾	Pass	

⁽¹⁾: N/A represents "Not Applicable".

Table 1 Results of Needle Safety Activation Force and Needle Safety Override Force

Needle Safety Activation Force					
Condition	Test Point	Sample Size per Test Point	Total Sample Size	Total Failure rate	Overall confidence/reliability
Long term aging (2-8°C)	T0	30	720	0%	(b) (4)
	1M	30			
	3M	30			
	6M	30			
	9M	30			
	12M	30			
Accelerated aging (25°C±2°C)	T0	30			
	1M	30			
	3M	30			
	6M	30			
	9M	30			
Simulated shipping	Before shipping	30			
	After shipping	30			
Free fall	N/A	30			

Needle Safety Override Force					
Condition	Test Point	Sample Size per Test Point	Total Sample Size	Total Failure rate	Overall confidence/reliability
Long term aging (2-8°C)	T0	60	870	0%	(b) (4)
	1M	60			
	6M	60			
Accelerated aging (25°C±2°C)	T0	60			
	1M	60			
	6M	60			
	9M	60			
Simulated shipping	Before shipping	60			
	After shipping	60			
Free fall	N/A	30			

Reviewer Comments:

The needle safety device for the HLX14 PFS is the Becton Dickinson (BD) Ultrasafe Plus Needle Safety Guard Assembly that is incorporated onto the pre-filled glass syringe on-site by the sponsor. The sponsor, Henlius, provided an image of the assembled PFS and needle safety device, schematics of the device, and a representative Certificate of Analysis from BD for the device referencing **DMF# 037027**.

Upon initial review, critical elements of essential performance requirements (EPRs) were not available in the submission. The sponsor only provided break loose force, glide force, and container closure integrity. The sponsor did not provide any EPR data related to the needle safety device per ISO 23908:2011. Needle Safety Activation force and did not include any data on the needle safety lockout force.

IR#1.

(b) (4)

(b) (4)

IR# 1.2

(b) (4)

(b) (4)

(b) (4)

IR#1.3,

(b) (4)

(b) (4)

**Information Request
#1.1**

(b) (4)

Sponsor Response	The sponsor provided Needle Safety Pre-Activation Force and Needle Safety Override Force. However, the sponsor did not provide Needle Safety Activation Force or statistical analysis for Needle Safety Override Force.
Reviewer Comments	A follow-up IR will be issued.
Response Adequate:	☐ Yes ☒ No, See IR # 1.1

Information Request #1.2	(b) (4)
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Sponsor Response	The sponsor sought clarification on IR#1.1 during an external sponsor call held on 02/11/2025. The sponsor clarified that the data presented (b) (4)
Reviewer Comments	While the sponsor provided the EPR data requested, the needle safety activation force and needle safety override force were not tested to ensure a confidence/reliability (b) (4) as requested in IR#1 and IR#1.1 per ISO 23908:2011.
Response Adequate:	☐ Yes ☒ No, See IR # 1.3

Information Request #1.3	(b) (4)
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	(b) (4)
Sponsor Response	In response to IR 1.3, the sponsor provided that they believe they reached a sample size commensurate to a confidence/reliability (b) (4) for each essential performance requirement by pooling the samples from each condition (e.g. fall, drop, accelerated aging, simulated shipping, etc.). Cumulatively the sponsor provided a sample size of n=720 for the needle safety activation force and n=870 for needle safety override force with zero failures.
Reviewer Comments	We usually recommend a sample size supported by confidence and reliability (b) (4) for each condition for the essential performance requirement of the needle safety device. To be least burdensome, the sponsor's reasoning that the pooling of samples to achieve a (b) (4) confidence and reliability is considered reasonable. A comment will be left for the sponsor recommending that they plan future test methods to include a sample size supported by (b) (4) confidence and reliability for each condition for each EPR for needle safety devices.
Response Adequate:	☒ Yes ☐ No

<<END OF REVIEW>>

5. APPENDIX A (INFORMATION REQUESTS)

(b) (4)



USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	March 24, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761444
Product Name, Dosage Form and Strength:	Bildyos ^a (denosumab-xxxx) ^b injection, 60 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Rx
Device Constituent:	Prefilled Syringe (PFS)
Applicant/Sponsor Name:	Shanghai Hanlius Biotech Inc. (SHB)
Submission Date:	August 30, 2024
OSE TTT #:	2024-10714
DMEPA 1 Safety Evaluator:	Keith Christopher, PhD
DMEPA 1 Team Leader:	Matthew Barlow, RN, BSN
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

1 REASON FOR REVIEW

The review evaluates the use-related risk analysis (URRA) and comparative analyses submitted under BLA 761444 for Bildyos (denosumab-xxxx) Prefilled Syringe (PFS) to determine whether Shanghai Hanlius Biotech Inc. (SHB) needs to submit human factors (HF) validation study results and comparative use human factors (CUHF) study results to support their future marketing

^a Bildyos has been developed as a proposed interchangeable biosimilar to US-licensed Prolia. At the time this review was written, the proprietary name, Bildyos, was conditionally approved for this proposed product on November 12, 2024. However, the proprietary name placeholder “HLX14” was used throughout the submission; therefore, we used HLX14, throughout the review.

^b The proposed nonproprietary name suffix has not been conditionally accepted. We therefore refer to the proposed product as “denosumab-xxxx” throughout this review in place of the nonproprietary name for this product.

application as a proposed biosimilar and interchangeable biosimilar to US-licensed Prolia (hereafter, called Prolia).

2 BACKGROUND

Bildyos (denosumab-xxxx) is a combination product in a single dose prefilled syringe (PFS) with a safety needle guard device constituent part and is intended to be administered by healthcare professionals. It is proposed to be indicated for the following, which is identical to Prolia:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

On January 24, 2024 SHB submitted a use-related risk analysis (URRA) and comparative analyses (physical comparison, comparative task analysis, and a labeling comparison) under IND 153872 for HLX14 to support their future marketing application as a proposed biosimilar to US-licensed Prolia prefilled syringe (PFS). On March 11, 2024, we reviewed the URRA and comparative analyses, and we determined that the “results of human factors validation study do not need to be submitted with your (SHB) future marketing application for HLX14 PFS as a proposed biosimilar to US-licensed Prolia (BLA 125320).” Additionally, we recommended the Applicant include instructions for the healthcare providers (HCPs) in section 2.4 of the proposed prescribing information (PI) and remove the proposed separate Instructions for Use (IFU). Furthermore, we informed the Applicant that if there are modifications to the proposed product user interface subsequent to our advice, to submit the list of changes made to the user interface (in tabular format) along with an updated URRA and CA in their future marketing application submission.

On August 30, 2024, the Applicant submitted their marketing application under BLA 761444, which included a tabulated list of the changes made to the proposed user interface (see Appendix D) since the prior review of their URRA CA under IND 153872. The changes included removing the stand-alone Instructions for Use (IFU), adding “Instructions for Administration of Prefilled Syringe with Needle Safety Guard” in Section 2.4 of the prescribing information (PI), adding the trade name to the container labels, carton labeling, and tray labeling, and updating the formula description on the carton and tray labeling. Based on our independent review of the aforementioned information, we determined that these labeling differences are unlikely to negatively impact user’s ability to complete the critical tasks needed to use this product safely and effectively in the context of a proposed interchangeable biosimilar product to Prolia. Therefore, we determine that these labeling differences do not warrant data from an HF or CUHF study.

3 CONCLUSION

Based on the aforementioned information, we have determined that Shanghai Hanlius Biotech Inc. does not need to submit HF validation study and comparative use human factors (CUHF) study results as part of their marketing application for HLX14 as a proposed biosimilar and interchangeable biosimilar to Prolia. We have no HF recommendations for this marketing application.

Additionally, we note that the DMEPA 1 nomenclature and labeling review team will evaluate the product specific label and labeling under a separate cover. Therefore, additional labeling recommendations may be forthcoming.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES AND HF-RELATED SUPPORTING DOCUMENTS

The use-related risk analysis (URRA) for Bildyos submitted on August 30, 2024 can be accessible in EDR via: <\\CDSESUB1\EVSPROD\bla761444\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporotic-fractures\5354-other-stud-rep\ta-and-urra\updated-urra-report-60mg-pfs-clean.pdf>

The comparative analyses for Bildyos submitted on August 30, 2024 can be accessible in EDR via: <\\CDSESUB1\EVSPROD\bla761444\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporotic-fractures\5354-other-stud-rep\ta-and-urra\updated-ta-report-60mg-pfs-and-us-prolia-clean.pdf>

Tabular list of changes to the user interface since the Agency's previous review and Justification for Excluding Human Factors Study for Bildyos submitted on August 30, 2024 can be accessible in EDR via: <\\CDSESUB1\EVSPROD\bla761444\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporotic-fractures\5354-other-stud-rep\ta-and-urra\tabular-listing-of-modifications-to-use-interface.pdf>

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

N/A

APPENDIX C. PRODUCT SAMPLES, LABELS, AND LABELING

C.1 Product Samples

The Sponsor did not provide product samples for our review.

C.2 List of Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error experiences with similar products, we reviewed the following HLX14 labeling submitted by SHB on October 10, 2024 and the side-by-side comparison of carton and contain labeling.

- Carton Labeling
 - o <\\CDSESUB1\EVSPROD\bla761444\0002\m1\us\114-labeling\draft\carton-and-container\hlx14-60mg-carton.pdf>
- Container Label
 - o <\\CDSESUB1\EVSPROD\bla761444\0002\m1\us\114-labeling\draft\carton-and-container\hlx14-60mg-container-label.pdf>
- Prescribing Information (image not shown) available in EDR via (PDF version):
 - o <\\CDSESUB1\EVSPROD\bla761444\0002\m1\us\114-labeling\draft\labeling\drafted-uspi-bildyos.pdf>

C.3 Labels and Labeling Images

Carton Label:



Container label:



APPENDIX D. TABULAR LIST OF CHANGES TO THE USER INTERFACE

Use interface		After Modification	Before Modification	Justification
Label	Prescribing information	Add “Instructions for Administration of Prefilled Syringe with Needle Safety Guard” in section 2.4 of prescribing information, which contain two-step use instructions with graphic illustration: Step1: Remove Needle Cap; Step 2: Administer Subcutaneous Injection.	(b) (4) (b) (4) the more detailed information is drafted for patient audience.	According to recommendation from FDA in PIND 153872, we remove (b) (4) (b) (4)
	Outer package	(b) (4)		Update Trade Name BILDYOS™
				Update Trade Name BILDYOS™

		(b) (4)		
		1. Update Trade Name BILDYOS™ 2. Update Description of formula according to current description in prescribing information		
		Update Trade Name BILDYOS™		
		Update Trade Name BILDYOS™		
		1. Update Trade Name BILDYOS™ 2. Update description of formula according to current description in prescribing information		
		Update Trade Name BILDYOS™		
Comparative task	Use steps	Two steps listed in current “Instructions for Administration of Prefilled Syringe	(b) (4)	Revise the use steps for instruction of healthcare professionals on preparation
		with Needle Safety Guard” in section 2.4 of prescribing information.		and administration of the prefilled syringe.

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/

KEITH G CHRISTOPHER
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03/24/2025 02:52:43 PM

JASON A FLINT
03/24/2025 02:54:29 PM