CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761439Orig1/Orig2s000

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:	September 3, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761439
Product Name, Dosage Form, and Strength:	Xtrenbo (denosumab-qbde) injection, 120 mg/1.7 mL (70 mg/mL)
Applicant Name:	Hikma Pharmaceuticals USA Inc. (Hikma)
FDA Received Date:	August 29, 2025
TTT ID #:	2024-11069-2
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

(b) (4) submitted revised container label and carton labeling received on August 29, 2025 for Xtrenbo. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Xtrenbo (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

(b) (4) implemented all of our recommendations and we have no additional recommendations at this time.

[a] Rahbani P. Review of Revised Label and Labeling for Xtrenbo (BLA 761439). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 Aug 19. TTT ID: 2024-11069-1

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

---

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/

PEGGY M RAHBANI
09/03/2025 01:23:39 PM

YEVGENIYA M KOGAN
09/04/2025 12:15:58 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)

*** 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 761439
Product Name, Dosage Form, and Strength:	Enoby (denosumab-qbde) injection, 60 mg/mL
Applicant Name:	Hikma Pharmaceuticals USA Inc. (Hikma)
FDA Received Date:	July 31, 2025
TTT ID #:	2024-11068-1
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

(b) (4) submitted revised container label and carton labeling received on July 31, 2025 for Enoby. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Enoby (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

(b) (4) implemented all of our recommendations and we have no additional recommendations at this time.

[a] Rahbani P. Review of Revised Label and Labeling for Enoby (BLA 761439). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 Jul 18. TTT ID: 2024-11068

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JULY 31, 2025

Container Label:

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

---

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/

PEGGY M RAHBANI
08/19/2025 04:12:05 PM

YEVGENIYA M KOGAN
08/20/2025 10:28:45 AM

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

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

Memorandum

Date: August 13, 2025

To: Sherry Hou, 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 ENOBY™ (denosumab-qbde) injection, for subcutaneous use

BLA: 761439

Background:
In response to DGE's consult request dated October 7, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide and carton and container labeling for the original BLA submission for ENOBY™ (denosumab-qbde) injection, for subcutaneous use.

PI and Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 4, 2025, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review for the ENOBY Medication Guide was 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 by the sponsor to the electronic document room on July 31, 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.

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

---

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/

MEENA R SAVANI
08/15/2025 12:29:09 PM

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

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

Memorandum

Date: August 8, 2025

To: Sherry Hou, 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 XTRENBO™ (denosumab-qbde) injection, for subcutaneous use

BLA: 761439

Background:
In response to DGE's consult request dated October 7, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original BLA submission for XTRENBO™ (denosumab-qbde) injection, for subcutaneous use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 4, 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 31, 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.

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

---

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/

JEENA L SUN
08/08/2025 11:16:20 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
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	August 6, 2025
To:	Sherry Hou Regulatory Project Manager **Division of General Endocrinology (DGE)**
Through:	Marcia Williams, PhD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Savani Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	DMPP and OPDP Concurrence with Submitted: Medication Guide (MG)
Drug Name (nonproprietary name):	ENOBY (denosumab-qbde)[1]
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761439
Applicant:	Hikma Pharmaceuticals USA

[1] Enoby (denosumab-qbde) has been developed as a proposed biosimilar to US-licensed Prolia (denosumab). The proposed proprietary name Enoby and denosumab-qbde were found to be conditionally acceptable on June 20, 2025, by the Division of Medication Error Prevention and Analysis I (DMEPA 1).

1 INTRODUCTION

On September 24, 2024, Hikma Pharmaceuticals USA, submitted for the Agency's review in accordance with Section 351(k) of the Public Health Service Act (PHS Act), a biosimilar interchangeable (RGB-14-P), Biologics License Application 761439 for Denosumab Injection, 60 mg/1 mL single-dose prefilled syringe. The proprietary name Enoby (denosumab-qdbe) was approved on June 20, 2025. Enoby (denosumab-qdbe) is indicated for the treatment:

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

The reference product that is the basis of this application as defined in the FDA's electronic Purple Book is Prolia® (Denosumab Injection), 60 mg/1 mL single-dose prefilled syringe registered by Amgen Inc. and approved under BLA 125320, License 1080.

On October 7, 2024, the Division of General Endocrinology (DGE) requested that the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) review the Applicant's proposed Medication Guide (MG) for Enoby (denosumab-qdbe).

This memorandum documents the DMPP and OPDP review and concurrence with the Applicant's proposed MG for Enoby (denosumab-qbde).

2 MATERIAL REVIEWED

- Draft Enoby (denosumab-qbde**)** MG received on September 27, 2024, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on August 4, 2025.
- Draft Enoby (denosumab-qbde**)** Prescribing Information (PI) received on September 27, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 4, 2025.
- Prolia (denosumab**)** MG approved May 22, 2025.

3 CONCLUSIONS

We find the Applicant's proposed MG is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP and OPDP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/

SHARON W WILLIAMS
08/06/2025 11:39:23 AM

MEENA R SAVANI
08/06/2025 12:15:16 PM

MARCIA B WILLIAMS
08/06/2025 12:18:38 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:	July 18, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761439
Product Name, Dosage Form, and Strength:	Enoby (denosumab- qbde) injection, 60 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Hikma Pharmaceuticals USA Inc. (Hikma)
FDA Received Date:	September 27, 2024, and November 1, 2024
TTT ID #:	2024-11068
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 Enoby (denosumab- qbde) injection, the Division of General Endocrinology (DGE) requested that we review the proposed Enoby Prescribing Information (PI), Medication Guide (MG), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

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 Enoby Prescribing Information (PI), Medication Guide (MG), container label, and carton labeling may be improved to promote the 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 Hikma Pharmaceuticals USA Inc. (Hikma) 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 and Medication Guide			
1.	We note a conditionally acceptable nonproprietary name suffix has been approved on June 20, 2025.	Revise the nonproprietary name on all labeling to incorporate the FDA-designated nonproprietary name suffix, “-qbde”, appended to the core name, “denosumab”, so that the proper name appears as “denosumab-qbde” throughout the labeling.	Replace the suffix placeholder “-xxxx” with the approved suffix “qbde”.

Table 2. Identified Issues and Recommendations for the Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		See Draft Guidance for Industry: Nonproprietary Naming of Biological Products: Update (March 2019).	
Highlights of Prescribing Information			
1.	The statement "Enoby should be administered by a healthcare (b) (4) needs to be revised.	For consistency across denosumab PIs	We recommend revising the "Enoby should be administered by a healthcare (b) (4) statement to "Enoby should be administered by a healthcare provider." and list this instruction as the first statement in the Dosage and Administration section for increased prominence.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The statement "Enoby should be administered by a healthcare (b) (4) needs to be revised.	For consistency across denosumab PIs	We recommend revising the "Enoby should be administered by a healthcare (b) (4) statement to "Enoby should be administered by a healthcare provider." and list this instruction as the first statement in the Dosage and Administration section for increased prominence.

5 RECOMMENDATIONS FOR HIKMA PHARMACEUTICALS USA INC. (HIKMA)

Table 3. Identified Issues and Recommendations for Hikma Pharmaceuticals USA Inc. (Hikma) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	We note a conditionally acceptable nonproprietary name suffix has been approved on June 20, 2025.	Should your BLA be approved during this review cycle, "denosumab-qbde" will be the proper name designated in the license. Revise the nonproprietary name on all labeling to incorporate the FDA-designated nonproprietary name suffix, "-qbde", appended to the core name, "denosumab", so that the proper name appears as "denosumab-qbde" 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 "qbde".
Container Label			
1.	The NDC number and route of administration statement appear prominent and compete with other critical information (e.g., proprietary name, established name, strength, etc.) on the principal display panel.	Critical product information should appear as the most prominent information on the PDP in accordance with 21 CFR 201.15.	We recommend decreasing the font size of the NDC number and unbolding and decreasing the font size of the route of administration statement, so they do not compete in size or prominence with critical information on the principal display panel.

Table 3. Identified Issues and Recommendations for Hikma Pharmaceuticals USA Inc. (Hikma) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
1.	As currently presented, the back panel appears nearly identical to the principal display panel (PDP) due to the presence of overlapping information (e.g., proprietary name, proper name, strength, route of administration, package type, etc.,)	Due to the back panel and the PDP appearing similar critical information may be missed that is typically displayed on the PDP.	We recommend removing information already on the PDP (e.g., proprietary name, established name, strength, product logo, product graphic, route of administration, etc.,) from the back panel. Consider limiting the PDP information to proprietary name, proper name, dosage form, strength, route of administration, Rx Only statement, net quantity statement, NDC, "Enoby should be administered by a healthcare provider" and medication guide statement. The remaining information (e.g., storage, "not made with natural rubber latex", etc.) can be placed on the back panel.
2.	The logo "hikma" is located in-line and in close proximity to the proprietary name and competes with critical information on the principal display panel (PDP) and other panels.	Due to the in-line location and prominence of the logo "hikma" it may be mistaken for the product name and may lead to confusion and medication errors. Furthermore, logo should not compete in size and prominence with critical information on the principal display panel.	We recommend relocating the logo "hikma" away from the proprietary name and on the PDP consider deleting the logo as it currently appears on the side panels. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

Table 3. Identified Issues and Recommendations for Hikma Pharmaceuticals USA Inc. (Hikma) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The Route of Administration and the "Not made with natural rubber latex" statements appear bolded and prominent.	Overuse of bold font may diminish its effect on prominence of other important product information on the PDP.	Consider unbolding the "For Subcutaneous Use Only" and the "Not made with natural rubber latex".
4.	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 as the entirety of the statement is bolded. Furthermore, the storage information appears on the PDP decreasing the available white space for overall readability.	Storage information should align with the PI. Additionally, lack of clarity and overuse of bolding might result in important storage information being overlooked. Furthermore, the storage statement contributes to the visual clutter on the PDP.	Revise the storage statement to read "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Enoby must not be exposed to temperatures above 25°C/77°F. Do not freeze. Avoid excessive shaking. Once removed from the refrigerator, Enoby must be used within 30 days. Discard Enoby if not used within the 30 days. Do not use Enoby after the expiry date printed on the label." and relocate the statement to the side or back panel.
5.	As presented the statement "Enoby 60 mg is administered once every 6 months" is inconsistent with the product strength of 60 mg/mL.	Inconsistent strength presentations may lead to wrong strength medication errors.	Revise the statement to read "Enoby 60 mg/mL injection is administered once every 6 months".
6.	The principal Display Panel (PDP) does not include the statement that Enoby 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.	On the PDP add the statement "Enoby should be administered by a healthcare provider." To make space for this statement on the PDP you may consider relocating the storage information and the statement

Table 3. Identified Issues and Recommendations for Hikma Pharmaceuticals USA Inc. (Hikma) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			"Not made with natural rubber latex" to the side/back panel.
7.	The terminology within the statement of dosage statement (b) (4) (b) (4) (b) (4) (b) (4) is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage statement to read, "Recommended Dosage: see Prescribing Information." on the back panel in accordance with 21 CFR 201.55
8.	The Medication Guide (MG) statement is located on a side panel.	Ensure the Medication Guide statement appears in accordance with 21 CFR 208.24(d).	Relocate the MG statement to the PDP and ensure it appears on the label in a prominent and conspicuous manner. To make space for this statement on the PDP you may consider relocating the storage information and the statement "Not made with natural rubber latex" to the side/back panel.
9.	The net quantity statement (b) (4) 60 mg single-dose prefilled syringe" is not expressed as total quantity per total volume, appears bolded, and has redundancy of information with the statement "Single-Dose Prefilled Syringe. Discard unused portion."	The product strength should be expressed as the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling. Furthermore, the overuse of bolding might result in important information being overlooked. Additionally, the redundancy of information contributes to the visual clutter on the PDP.	Express the product strength as total quantity per mL in accordance with USP General Chapter <7>. We recommend the net quantity statement to read "One 60 mg/mL Single-Dose Prefilled Syringe." Furthermore, we recommend unbolding and relocating the net quantity statement to the bottom left/right of the carton PDP and combining the net quantity statement and the "Single-Dose Prefilled Syringe. Discard unused portion" to read "One 60 mg/mL Single-

Table 3. Identified Issues and Recommendations for Hikma Pharmaceuticals USA Inc. (Hikma) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			Dose Prefilled Syringe. Discard unused portion." Additionally, you may consider removing any other net quantity statements from the carton as they are redundant and may be contributing to the visual clutter of the various panels.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Enoby received on November 1, 2024, from Hikma Pharmaceuticals USA Inc. (Hikma). Enoby (denosumab- qbde) is a proposed biosimilar and interchangeable to US-licensed Reference Product, Prolia (denosumab) BLA 125320.

Table 4. Relevant Product Information for Enoby (denosumab- qbde) injection and US-licensed Prolia

Product Name	Enoby	Prolia[a]
Initial Approval Date	N/A	June 1, 2010
Active Ingredient	Denosumab- qbde	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.	
Route of Administration	Subcutaneous	
Dosage Form	injection	
Strength	60 mg/mL	
Dose and Frequency	60 mg subcutaneous injection once every 6 months	
How Supplied	60 mg/mL single-dose prefilled syringe with a safety guard. The prefilled syringe is not made with natural rubber latex.	60 mg/mL single-dose prefilled syringe.
Storage	Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Prior to	Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once

[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

	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.	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	

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 Enoby labels and labeling submitted by Hikma Pharmaceuticals USA Inc. (Hikma).

- Prescribing Information and Medication Guide (MG) received on November 1, 2024, available from \\CDSESUB1\EVSPROD\bla761439\0003\m1\us\114-labeling\draft\labeling\1ml-proposed-insert-track-changes-word.docx
- Container label received on September 27, 2024
- Carton labeling received on September 27, 2024

B.2 Container Label and Carton Labeling Images

Container Label:

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

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

---

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/

PEGGY M RAHBANI
07/21/2025 11:24:49 AM

YEVGENIYA M KOGAN
07/21/2025 12:34:50 PM

M E M O R A N D U M

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

DATE: July 16, 2025

TO: Theresa Kehoe, MD
Director
Division of General Endocrinology
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Pharmacologist
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Rubén C. Ayala, Pharm.D.
Lead Pharmacokineticist
DNDSI, OSIS.

SUBJECT: Review of analytical inspection of (b) (4)

(b) (4)

1. Inspection Summary

OSIS inspected the analytical portion of pharmacokinetic study RGB-14-001 (BLA 761439, RGB-14 [Denosumab]) conducted at the (b) (4)

Objectionable conditions were not observed, discussion items were not conveyed, and Form FDA 483 was not issued at the inspection close-out. Based on the inspection findings, there are no identified concerns regarding the reliability of audited concentration data from study RGB-14-001.

2. Inspected Study:

BLA 761439

Study Number: RGB-14-001
Study Title: "Randomized, double-blind, single, 60 mg fixed dose, parallel comparative pharmacokinetic and pharmacodynamic (Phase 1) study of RBG-14-X and Xgeva in healthy adult male subjects."

Dates of Pharmacokinetic Sample Analysis: 9/8/2021 to 8/22/2023

Analytical site: (b) (4)

FEI #: (b) (4)

3. Inspection Scope

OSIS Scientist Gajendiran Mahadevan, Ph.D. inspected the analytical portion of pharmacokinetic study RGB-14-001 conducted at the (b) (4) (b) (4) on (b) (4) (b) (4) and (b) (4)

3.1 Previous Inspection

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

3.2 Current Inspection

The current inspection included a tour of analytical-relevant areas, examination of pharmacokinetic study records including method validation and sample analyses, examination of instrument calibration records, review of standard operating procedures (SOPs), review of training records, and interviews of site employees.

3.3 Inspection finding

At the conclusion of the inspection, I did not observe any objectionable conditions, issue Form FDA 483, or convey discussion items to site management.

Gajendiran Mahadevan, Ph.D.
Pharmacologist

Draft: GM 7/15/2025
Edit: RCA 7/15/2025

OSIS File #: (b) (4)

eNSpect Assignment ID: (b) (4)
eNSpect Op ID: (b) (4)

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/

GAJENDIRAN MAHADEVAN
07/16/2025 02:27:40 PM

RUBEN C AYALA
07/16/2025 02:39:55 PM

M E M O R A N D U M

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

DATE: July 11, 2025

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

FROM: Monica Javidnia, 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 Parexel Early Phase Clinical Unit, Harrow, United Kingdom

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of study RGB-14-001 (BLA 761439) conducted at Parexel Early Phase Clinical Unit, Harrow, United Kingdom. The OSIS Review for a second site, Nuvisan GmbH (Neu-Ulm) was completed 07/10/2025.

Form FDA 483 was issued at Parexel Early Phase Clinical Unit for destroying the paper code break emergency envelopes per sponsor request. There were no discussion items. Based on the inspection findings, there are no identified concerns for Parexel Early Phase Clinical Unit regarding reliability of the data or human subject protection for inspected study RGB-14-001 for the review division consideration.

2. Inspected Study

BLA 761439

Study Number: RGB-14-001

Study Title: "Randomised, Double-Blind, Single, 60 mg Fixed Dose, Parallel Comparative Pharmacokinetic and Pharmacodynamic (Phase 1) Study of RGB-14-X and Xgeva® in Healthy Adult Male Subjects"

Dates of study conduct: 01/15/2021 – 07/06/2023

Clinical site: Parexel Early Phase Clinical Unit (London)
Northwick Park Hospital
Watford Road
Harrow, HA1 3UJ
United Kingdom
CI: Pablo Forte-Soto, M.D., Ph.D.

3. Inspectional Findings

Parexel Early Phase Clinical Unit, Harrow, United Kingdom

OII investigator Richard Berning inspected Parexel Early Phase Clinical Unit (London), Northwick Park Hospital, Watford Road, Harrow, HA1 3UJ, United Kingdom from April 29 - May 02, 2025.

3.1 Previous Inspection

The previous OSIS inspection of Parexel Early Phase Clinical Unit was conducted from December 07-11, 2015. At the conclusion of the inspection, Form FDA 483 was not issued. There was one discussion item due to not retaining the blinding codes, per the sponsor's instruction. Form FDA 483 was issued during the current inspection for a similar issue (see section 3.3.1).

3.2 Current Inspection

The current inspection included auditing the following items:

-Training records
-Subject records (19 subjects)
-Electronic platform (ClinBase)
-Randomization
-Investigational product records
-Study-related correspondence

3.3 Inspection Findings

At the conclusion of the inspection, investigator Berning observed objectionable conditions and Form FDA 483 was issued to the clinical site. The Form FDA 483 observation(s) (**Attachment**

1), the firm's response dated 05/22/2025 (**Attachment 2**), and my evaluation are presented below.

3.3.1 FDA 483 Observations

Observation 1: You failed to maintain adequate case histories with respect to the conduct of the study.

Specifically,

This study relied on paper code break envelopes to use in the event of the need for emergency unblinding of a subject's treatment. These documents were all destroyed on 18 October 2023 after the closure of the study at your site. Due to this destruction of original study documentation, I was unable to verify that none of these blind break envelopes were used during the study period as per other documentation at your study site.

OSIS Evaluation: I reviewed the code break envelope-related documents provided by OII and the firm, demonstrating that the envelopes were kept intact throughout the study. There is no evidence blinding was compromised during the study. In addition, OII verified all subjects were dosed per the randomization schedule.

While OII was unable to break the blinding during the inspection, maintaining the code break envelop is not required by the protocol, and OII did not identify any issues in dosing documentations. Therefore, I conclude that this finding does not raise concerns about the site's conduct of the study and is unlikely to impact data reliability. However, the review division may, at its discretion, inquire blind-breaking information for the inspected sites (Parexel and Nuvisan) from the sponsor.

Firm's Response: The firm's standard operating procedure is to archive the envelopes at the completion of the study, which was broken in this situation at the request of the sponsor.

Attachments
Attachment 1: Form FDA 483 to Parexel
Attachment 2: Parexel response to Form FDA 483

Monica Javidnia, Ph.D.
Pharmacokineticist

Draft: MJ 07/11/2025
Edit: JC 07/11/2025

OSIS File #: BE 10453

eNSpect Assignment ID: 257445
eNSpect OpID: 308882 (Parexel Early Phase Clinical Unit)

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/

MONICA JAVIDNIA
07/11/2025 03:11:55 PM

SEONGEUN CHO
07/14/2025 07:10:45 AM

M E M O R A N D U M

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, MD
Director
Division of General Endocrinology (DGE)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Office of New Drugs (OND)

FROM: Monica Javidnia, 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 Nuvisan GmbH, Neu-Ulm, Bavaria, Germany

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of study RGB-14-001 (BLA 761439) conducted at Nuvisan GmbH, Neu-Ulm, Bavaria, Germany.

Form FDA 483 was issued at Nuvisan GmbH for destroying the paper code break emergency envelopes (Observation 1a) and lack of documentation that subjects were supine for five minutes prior to supine blood pressure measurement (Observation 1b). Based on the inspection findings, there are no identified concerns for Nuvisan GmbH, Neu-Ulm regarding reliability of the data or human subject protection for inspected study RGB-14-001 for the review division consideration.

2. Inspected Study

BLA 761439

Study Number: RGB-14-001

Study Title: "Randomised, Double-Blind, Single, 60 mg Fixed Dose, Parallel Comparative Pharmacokinetic and Pharmacodynamic (Phase 1) Study of RGB-14-X and Xgeva® in Healthy Adult Male Subjects"

Dates of study conduct: 01/15/2021 – 07/06/2023

Clinical site: Nuvisan GmbH
Site Neu-Ulm
Wegenerstrasse 13
89231 Neu-Ulm
Bavaria, Germany
CI: Michael Lissy, M.D.

3. Inspectional Findings

Nuvisan GmbH, Neu-Ulm, Germany

OII investigator Karen Montgomery inspected Nuvisan GmbH, Site Neu-Ulm, Wegenerstrasse 13, 89231 Neu-Ulm, Germany from May 05-09, 2025.

3.1 Previous Inspection

The previous OSIS inspection at Nuvisan GmbH (CI: Michael Lissy) was conducted from April 24-26, 2023 (study conducted at Nuvisan in Gauting, but study documents and reserve samples were kept in Nuvisan Neu-Ulm). At the conclusion of the inspection, Form FDA 483 was not issued. There was one discussion item for a protocol deviation, dosing less than 30 minutes after breakfast. The final classification was VAI. Corrective actions were not confirmed during the current inspection. Please note the current inspection was at a different Nuvisan site than for the previously inspected study.

3.2 Current Inspection

The current inspection included auditing the following items:

-Subject eligibility
-Investigational product records, including dosing and reserve samples
-Training logs
-Ethics committee approvals
-Randomization
-Subject records, including adverse events, concomitant medications, land laboratory values

3.3 Inspection Findings

At the conclusion of the inspection, investigator Montgomery observed objectionable conditions and Form FDA 483 was issued to the clinical site. The Form FDA 483 observation(s) (**Attachment 1**), the firm's response dated 05/30/2025 (**Attachment 2**), and my evaluation are presented below.

3.3.1 FDA 483 Observations

Observation 1: Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Specifically,

A) This study relied on sealed paper code break emergency envelopes to be use in the event of a subject's treatment needing to be unblinded. The code break emergency envelopes maintained at your site during the course of this study were destroyed on 02May2024 after the study was closed out on 07Oct2023. Because of this, I was unable to verify that the seals on the envelopes were maintained. I was also unable to verify the envelopes contained the correct subject randomization assignment when compared to the unblinded randomization schedule.

B) The vitals section of the protocol required that supine blood pressure and pulse measurements were to be taken at every study visit after the subject had rested in a supine position for at least 5 minutes in a quiet setting without distractions. For all 26 of the 26 enrolled subjects, the source paper casebooks and the electronic case report forms do not document if subjects were in a supine position for at least 5 minutes without distraction prior to these measurements being taken. This affected every vitals measurement collected for every visit when vitals were measured for the entirety of this study.

OSIS Evaluation:

A) I reviewed the documentation (communications between site and sponsor and envelope-related documents) provided by OII and the firm, demonstrating that the envelopes were kept intact throughout the study. There is no evidence blinding was compromised during the study.

While OII was unable to break the envelopes and compare the codes to the randomization schedule, OII verified all subjects

were dosed per the randomization schedule. This item does not impact data reliability.

B) Per the protocol, supine blood pressure measurements were to be taken after 5 minutes in the supine position in a quiet setting with no distractions. OII noted records from all 26 enrolled subjects did not include denotation of the start of entering the supine position. As the protocol did not specify that the time of entering the supine position be recorded, and the subject record provided (15021) did not include a line to record this information, this item does not impact data reliability.

Firm's Response:

(A) The code break envelopes were kept sealed and intact throughout the study (verified at a close out monitoring visit) and were destroyed at the request of the sponsor.

(B) The CI provided their work instruction and general study schedule, both stating the vitals are taken after 5 minutes in the supine position.

Attachments
Attachment 1: Form FDA 483 to Nuvisan
Attachment 2: Nuvisan response to Form FDA 493

Monica Javidnia, Ph.D.
Pharmacokineticist

Draft: MJ 07/03/2025, 07/10/2025
Edit: MO 07/08/2025; JC 07/09/2025 7/10/2025

OSIS File #: BE 10453

eNSpect Assignment ID: 257445
eNSpect OpID: 308881 (Nuvisan, GmbH)

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/

MONICA JAVIDNIA
07/10/2025 01:24:34 PM

MEI OU
07/10/2025 01:25:21 PM

SEONGEUN CHO
07/10/2025 01:40:47 PM

M E M O R A N D U M

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

DATE: June 2, 2025

TO: Theresa Kehoe, MD
Director
Division of General Endocrinology
Office of New Drugs

FROM: Melkamu Getie-Kebtie, Ph.D., R.Ph.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH:
Stanley Au, Pharm.D., BCPS
Lead Pharmacokineticist
DGDSI
OSIS

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

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical inspection of study RGB-14-001 (BLA 761439, RGB-14-P and RGB-14-X [a proposed biosimilar to denosumab/Prolia® and denosumab/Xgeva®]) conducted at (b) (4)

Objectionable conditions were found during the inspection and Form FDA 483 was issued at the inspection close-out. Based on the inspection observations, exhibits, and the firm's response to Form FDA 483, the sCTx concentration data from samples listed in 3.3.1 below are unreliable. In addition, concentration values below the limit of quantitation of the assay (i.e., 0.05 ng/mL) are not reliable. I recommend that the review division exclude these data from the pharmacodynamic (PD) analysis.

Please note corrections to the bioanalytical report for sCTx mentioned in section 3.3.2.2.

2. Inspected Study

BLA 761439
Study Number: RGB-14-001
Study Title: "Randomised, Double-Blind, Single, 60 mg Fixed Dose, Parallel Comparative Pharmacokinetic and Pharmacodynamic (Phase 1) Study of RGB-14-X and Xgeva® in Healthy Adult Male Subjects"
Dates of sample analysis: 2/16/2021 – 7/13/2023

3. Inspectional Findings

OSIS Scientist Melkamu Getie-Kebtie inspected [redacted] from [redacted]

3.1 Previous Inspection

This was the first OSIS inspection of [redacted] under the BA/BE program.

3.2 Current Inspection

The current inspection included auditing study related records and interviewing the firm's management and staff.

3.3 Inspection finding

At the conclusion of the inspection, I observed objectionable conditions and Form FDA 483 was issued to the analytical site. No discussion item was presented. The Form FDA 483 observations (**Attachment 1**), the firm's response dated 5/28/2025 (**Attachment 2**), and my evaluation are presented below.

3.3.1 FDA 483 Observations

[redacted]

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Attachment(s)
Attachment 1: Form FDA 483
Attachment 2: Response to Form FDA 483
Attachment 3: Note describing error in the bioanalytical report

Melkamu Getie-Kebtie, R.Ph., Ph.D.,
Pharmacologist

Draft: MG 5/29/2025, 5/30/2025, 6/2/2025
Edit: SA 05/29/2025, 5/30/25, 6/2/2025

OSIS File #: BE (b) (4)

AMS Assignment ID: (b) (4)
eNSpect OpID: (b) (4)

61 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

MELKAMU GETIE KEBTIE
06/02/2025 02:36:44 PM

STANLEY AU
06/02/2025 03:59:38 PM

Clinical Inspection Summary

Date	May 7, 2025
From	Courtney McGuire, MD, Primary Reviewer Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Sooyoung Lim, MD, Clinical Reviewer Shivangi Vachhani, MD, Clinical Team Leader Sherry Hou, PharmD, RPM reviewer Division of General Endocrinology (DGE)
BLA #	761439
Applicant	Hikma Pharmaceuticals USA, Inc.
Drug	RGB-14-X (denosumab), 120 mg/1.7 mL in vial; proposed biosimilar to Xgeva RGB-14-P (denosumab), 60 mg/1 mL in prefilled syringe; proposed biosimilar to Prolia
NME (Yes/No)	No (biosimilar, 351[k])
Therapeutic Classification	Receptor activator of nuclear factor (RANKL) inhibitor
Proposed Indication	Treatment of postmenopausal women with osteoporosis at high risk for fracture.
Consultation Request Date	November 14, 2024
Summary Goal Date	July 25, 2025
Action Goal Date	September 26, 2025
BsUFA Date	September 27, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Hikma Pharmaceuticals USA, Inc., submitted clinical data from the Phase III study (Protocol RGB-14-101 [NCT05087030]) and the Phase I study (Protocol RGB-14-001) to the Agency in support of a Biological Licensing Application (BLA 761439) for two biosimilar products, RGB-14-X and RGB-14-P, proposed for the following indications:

RGB-14-P (denosumab injection, 60 mg/1 mL prefilled syringe), a drug-device combination product, as a biosimilar product to the reference product, Prolia, approved for:

- 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.

RGB-14-X (denosumab injection, 120 mg/1.7 mL in a single-dose vial), as a biosimilar product to the reference product, Xgeva, approved for

- 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.

The Phase III study (Protocol RGB-14-101) was selected for Good Clinical Practice (GCP) inspections. Three foreign clinical investigators (CIs), Drs. Sylva Brtniknova (Site 4207), Paulina Ludziak (Site 4825), and Katarzyna Bartnicka-Maslowska (Site 4824), and the imaging Contract Research Organization (CRO), (b) (4) were inspected.

The inspections of three CIs, Drs. Brtniknova, Ludziak, and Bartnicka-Maslowska, did not find significant concerns regarding the study conduct, data integrity, GCP, or regulatory compliance. The inspection of the imaging CRO (b) (4) revealed no significant concerns regarding the conduct of the imaging review, data discrepancies or integrity, regulatory compliance, or GCP. Based on these inspections, data generated by the inspected CIs and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indications.

II. BACKGROUND

On September 27, 2024, Hikma Pharmaceuticals USA, Inc. submitted biosimilar interchangeable BLA 761439 seeking approval of the following two biosimilar products:

RGB-14-P (denosumab injection, 60 mg/1 mL prefilled syringe), a drug-device combination product, as a biosimilar product to the reference product, Prolia, approved for:

- 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.

RGB-14-X (denosumab injection, 120 mg/1.7 mL in a single-dose vial), as a biosimilar product to the reference product, Xgeva, approved for

- 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.

Denosumab, the active substance of both Prolia and Xgeva, is a human monoclonal antibody that targets and binds with high affinity and specificity to the receptor activator of nuclear factor (RANKL), preventing activation of its receptor (RANK) on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption in cortical and trabecular bone.

The primary evidence of safety and efficacy for RGB-14-P for the proposed indications and the focus of the BIMO inspections was a single phase 3 trial, Study RGB-14-101, evaluating RGB-14-P.

Study Design

Study RGB-14-101 was a phase 3, randomized, double-blind, multicenter, 2-arm, parallel-group study designed to assess the efficacy, pharmacodynamics, safety, tolerability, and immunogenicity of RGB-14-P versus Prolia in subjects with postmenopausal osteoporosis. The study consisted of a 35-day Screening Period, a 52-week Main Period, and an optional 52-week Transition Period.

Following the 35-day Screening Period, eligible subjects were equally randomized to receive RGB-14-P or Prolia in the 52-week Main Period. Subjects not entering the Transition Period completed an End-of-Study (EOS) Visit at Week 52. A subset of participants completing the Main Period were re-randomized at Week 52 (1:1) to receive either RGB-14-P or Prolia in a double-blinded manner during the optional Transition Period.

Endpoints

- *Primary endpoint*: Percent change from baseline (%CfB) in lumbar spine bone marrow density (BMD, g/cm2) at Week 52, where:

$$\%\text{CfB} = \frac{BMD_{WeekXX} - BMD_{Baseline}}{BMD_{Baseline}} * 100$$

BMD was measured by dual energy X-ray absorptiometry (DXA) and read by a central imaging CRO.

Study Status
The study enrolled the following subjects across 63 study centers, across 8 countries in Europe and North America, including 20 subjects enrolled across 3 sites in US.

Safety population: N = 473
Efficacy population: N = 473

Dr. Brtnikova (Site 4207), Dr. Ludziak (Site 4825), Dr. Bartnicka-Maslowska (Site 4824), and the imaging CRO (b) (4) were selected for inspection.

RESULTS

1. Sylva Brtnikova (Site 4207, Study RGB-14-101)
   28. rijna 3348/65
   Ostravaměsto, Ostrava, 702 00
   Czech Republic

Inspection Dates: February 24, 2025, to February 28, 2025

This CI was inspected as a comprehensive, review-based inspection for Study RGB-14-101. This was the first FDA inspection for this CI.

The site screened a total of 51 subjects, of which 30 were enrolled and randomized at the site. Two subjects discontinued early.

The inspection reviewed the following subject-related source documents for all 30 randomized subjects: signed informed consent forms (ICFs), eligibility and screening documents, subject charts, medical records, concomitant medications (CM), safety labs (random sampling), and adverse events (AEs).

The inspection also reviewed the following study-related documents: study protocol, signed statement of investigator forms, financial disclosures, curriculum vitae (CV), Site Signature and Delegation log, ICFs, ethics committee approvals, investigational product (IP) accountability logs, temperature logs, training records, communication documents, protocol deviation (PD) logs, and Screening and Enrollment logs.

There was no evidence of under-reporting of AEs, serious adverse events (SAEs), or PDs.

DXA scans supporting the primary efficacy endpoint were performed according to protocol and submitted to the central imaging CRO for BICR.

Based on the results of the inspection, Study RGB-14-101 data generated at Dr. Brtnikova's site appear acceptable in support of the proposed indication in the BLA.

2. Dr. Paulina Ludziak (Site 4825, Study RGB-14-101)
   Future Meds Wroclaw
   ul. Legnicka 16
   Wroclaw, Slaskie, 53-673
   Poland

Inspection Dates: 02/17/2025, to 02/21/2025

This CI was inspected as a comprehensive, review-based inspection for Study RGB-14-101. This was the first FDA inspection for this CI.

There were 48 subjects screened and 22 subjects enrolled and randomized. Twenty subjects completed the study.

The inspection reviewed subject-related source documents contained in study binders and CRFs for a sampling of 12 enrolled subjects.[1] The CRFs included randomization forms, visit notes, questionnaires, procedure details, laboratory results, IP labeling / inserts, and concomitant medications. The subject study binders contained case study files including consenting history, screening data, inclusion and exclusion eligibility, IP accountability, treatment records, and BICR imaging results.

Study-related records reviewed included but were not limited to protocols and amendments, ICFs, financial disclosure forms, Investigator Agreements, Delegation of Authority document, CVs, medical licenses, organizational chart, ethics committee approvals and correspondences, Future Med Standard Operating Procedures (SOPs), monitoring SOPs and reports, site training logs, imaging guidelines and review manuals, study blinding procedures, Sponsor communications, PD logs, AE logs, IP storage, electronic systems, and recruitment procedures.

There was no evidence of under-reporting of SAEs/AEs, PDs, or CMs based on source data reviewed.

DXA scans supporting the primary endpoint were performed according to protocol and submitted to the imaging CRO for BICR. Central read reports for BMD scores at Screening and Week 26 (locally filed copies) were verified against the data line listings.

The inspection identified one finding related to IP management:

- Study subject (b) (6) was randomized on (b) (6), but IP was administered on (b) (6) because the site did not have sufficient IP available on (b) (6).

  Reviewer comment. The inspection did not identify any concerns with IP storage conditions

[1] Subject IDs: (b) (6) (b) (6)

associated with the delay. Review of IP administration records for all subjects in both arms dosed at the site between (b) (6)*, did not appear to indicate potential for unblinding. The blinded site staff were unaware of what IP was required for each study subject and were not aware of specific inventory levels of RGB-14-P and Prolia. Overall, the delay does not appear to impact the interpretation of safety or efficacy.*

Based on the results of the inspection, the data generated at Dr. Ludziak's site appear acceptable in support of the proposed indication in the BLA.

3. Dr. Katarzyna Bartnicka-Maslowska (Site 4824, Study RGB-14-101)
   Ul. Gruszowa 2
   Lodz, Lodzkie, 91-363
   Poland

Inspection Dates: March 31, 2025, to April 1, 2025

This investigator was inspected as a comprehensive, review-based inspection for Study RGB-14-101. This was the first FDA inspection for this investigator.

There were 22 subjects screened and 20 subjects enrolled and randomized.

The inspection reviewed subject-related source documents including ICFs for all 22 screened subjects, and subject case histories maintained in individual binders for all 20 randomized subjects, including but not limited to eligibility checklists, visit notes, laboratory reports (spot check), adverse event logs, progress notes, concomitant medication reports, physician imaging orders, DXA reports, Interactive Web Response System assignments, and IP dosing sheets.

Study-related records reviewed included FDA 1572 forms, Site Signature and Delegation Log, Declaration of Investigator forms, CVs, financial disclosures, Screening and enrollment logs, protocol and amendments, Ethics Committee approvals, ICFs forms, Authorization of DXA vendor, IP accountability / storage / disposition, and monitoring logs and communications.

DXA scans supporting the primary endpoint were performed according to protocol and submitted to the central reader for BICR. Central read reports for vertebral BMD scores (locally filed copies) were verified against the data line listings.

There was no evidence of under-reporting of AEs or protocol violations based on source data reviewed. The site's records were organized, complete, and accurately reported into the eCRFs. The inspection revealed no concerns with accuracy or reliability of the data. There was no evidence of unblinding.

Based on the results of the inspection, the data generated at Dr. Bartnicka-Maslowska's site appear acceptable in support of the proposed indication in the BLA.

4. (b) (4)

Inspection dates: (b) (4)

(b) (4) was inspected as a directed, review-based inspection for Study RGB-14-101. The firm was last inspected in (b) (4) without significant findings.

The inspection reviewed (b) (4) responsibilities to perform BICR of DXA scans for Study RGB-14-101. Records reviewed included the firm business history, Organizational Charts, contracts, and the DXA Independent Review Manual. The review found the processes adequate.

The inspection verified the primary efficacy endpoint for a random selection of 25 study subjects from clinical sites 4207, 4824, and 4825 by comparison of BMD Measurements for L1-L4 Vertebra, Lumbar Spine, and DXA scanner calibration data at the CRO with that of the data listings. There were no discrepancies identified.

Based on the results of the inspection, the imaging review data generated by (b) (4) appear acceptable in support of the proposed indication in the BLA.

{See appended electronic signature page}

Courtney McGuire, M.D.
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief

Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Review Division/ Division Director / Theresa Kehoe
Review Division/ Associate Director for Ther / Christy Osgood
Review Division/Project Manager/ Sherry Hou
Review Division/Clinical Team Lead/ Shivangi Vachhani
Review Division/Clinical Reviewer/ Sooyoung Lim
OSI/Office Director/David Burrow
OSI/GCP Program Analysts/Yolanda Patague

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/

COURTNEY S MCGUIRE
05/07/2025 11:55:35 AM

MICHELE B FEDOWITZ
05/07/2025 12:01:10 PM

JENN W SELLERS
05/07/2025 12:19:09 PM

MEMORANDUM

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 19, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761439
Product Type:	Combination Product (Drug-Device)
Product, Name, Dosage Form and Strength:	Enoby[a] (denosumab-xxxx)[b] injection, 60 mg/mL
Device Constituent:	Prefilled Syringe (PFS)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Hikma Pharmaceuticals USA Inc. (Hikma)[c]
FDA Received Date:	September 27, 2024; November 18, 2024
OSE TTT #:	2024-11107
DMEPA 1 Safety Evaluator:	Florence Mwangi, PharmD
DMEPA 1 Team Leader:	Matthew Barlow, RN, BSN
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES

[a] RGB-14-P has been developed as a proposed interchangeable biosimilar to US-licensed Prolia. The proprietary name Enoby was found conditional acceptable by DMEPA on November 04, 2024. Hikma refers to the product as "RGB-14-P throughout their submission; therefore, for the purposes of this review, "RGB-14-P" is used throughout the review to refer to this product.

[b] The nonproprietary name suffix for this IND has not yet been determined. Therefore, the placeholder "denosumab-xxxx" is used to refer to the non-proprietary name for this product and is not intended to be included in the final labels and labeling.

[c] On August 29, 2024, and September 06, 2024, the Applicant submitted an Administrative change/Sponsor and change in ownership of the application. Specifically, all applicable IND-related documentation for RGB-14-P was transferred from Gedeon Richter to Hikma Pharmaceuticals USA Inc. as of August 1, 2024.

1 REASON FOR REVIEW

On September 27, 2024, the Applicant submitted Biologics License Application (BLA) 761439 that included a usability risk assessment (hereafter referred to as a use-related risk analysis), threshold analysis (hereafter referred to as comparative analyses), and their justification for not submitting comparative use human factors (CUHF) study results to support their marketing application for RGB-14-P 60 mg/mL prefilled syringe (PFS) as a proposed interchangeable biosimilar to US-licensed Prolia (hereafter referred to as Prolia) PFS. Of note, we previously reviewed the use-related risk analysis, comparative analyses, and justification for RGB-14-P 60 mg/mL PFS as a proposed biosimilar to Prolia under IND 146025 and determined that the Applicant did not need to submit HF validation study results to support their future marketing application.[d]

2 BACKGROUND

RGB-14-P is a single ingredient combination product with a single-dose prefilled syringe device constituent part, intended for administration by healthcare professionals. RGB-14-P is a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor proposed for:

- 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 October 15, 2019, the Applicant submitted Biosimilar Biological Product Development (BPD) Type 2 meeting request under IND 146025 for RGB-14-P and RGB-14-X as proposed biosimilars to Prolia and US-licensed Xgeva, which included the following HF question: "*Does FDA agree that data from a comparative use human factors studies will not be necessary to support approval of RGB-14-p due to the high similarity between the user interface of US-licensed Prolia and as a consequence that the Sponsor's proposed procedural plan of the threshold analysis of the RGB-14-p combinational product to the Agency is appropriate*?" Additionally, the Applicant submitted the Comparative Analysis (CA) as part of the meeting package. In the meeting minutes dated January 17, 2020, we informed the Applicant that it was premature to answer the question and recommended that the Applicant submit their CA, URRA, and justification for not conducting a HF validation study for review as separate submissions to the IND.[e]

---

[d] Kogan, Y. Use-Related Risk Analysis and Comparative Analyses review for RGB-14-P (denosumab) Injection, 60 mg/mL (IND 146025). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);22 MAR 2024. TTT No.: 2023-4930

[e] Bell, S. Meeting Minutes for IND 146025, denosumab-xxxx (RGB-14-P). Silver Springe (MD): FDA, CDER, OND (DGE); 2020 JAN 17

On August 3, 2020, the Applicant requested a Type B/Pre-IND meeting request under IND 146025 to seek the Agency feedback regarding their biologic development program for RGB-14-P, a proposed biosimilar to Prolia. In the final written response letter dated October 16, 2020, we reiterated our recommendation that the Applicant submit a comprehensive URRA, CA, and justification for not conducting a HF validation study.[f]

On July 7, 2023, the Applicant submitted a URRA, CA, and justification for not submitting HF validation study results under IND 146025 for RGB-14-P 60 mg/mL PFS to support their future marketing application as a proposed biosimilar to Prolia. On March 22, 2024, we reviewed the URRA, CA, and justification and determined that the Applicant does not need to submit HF validation study results to support their future marketing application. We also advised the Applicant that they will need to submit an updated URRA with a determination for HF data requirements for Agency review if they modified their product user interface.[g]

On September 27, 2024, the Applicant submitted BLA 761439 for RGB-14-P 60 mg/mL PFS as a proposed interchangeable biosimilar to Prolia. This submission included their URRA and CA~~,~~ for RGB-14-P 60 mg/mL PFS. However, it was not clear if the URRA, CA, and product user interface, of the proposed RGB-14-P 60 mg/mL PFS presentation submitted on September 27, 2024, under BLA 761439 was the same as the URRA, CA, and product user interface submitted for review on July 7, 2023, under IND 146025. Thus, we issued an information request (IR) to the Applicant on November 14, 2024, to clarify.[h]

Subsequently, on November 18, 2024, the Applicant identified the changes made to the CA and product user interface since our previous review along with their rationale as to why additional HF data is still not warranted. The Applicant indicated that they made the following changes to the CA since our March 22, 2024, review[i]:

- Added the section "*use specification comparison*" of the intended use, users, use environment, and specification listed in the product description of the Prolia PFS and RGB-14-P to "*illustrate the identical nature of the two products in this regard*."
- Updated the comparison task analysis to include the task "*Administer next dose after 6 months.*"
- Updated the secondary packaging section to include the patient reminder card as required "instructional materials."
- Updated the labeling comparison to include the patient reminder card.

---

[f] Kiani, S. Final Written Response for IND 146025, denosumab-xxxx (RGB-14-P). Silver Spring (MD): FDA, CDER, OND (DGE); 2020 OCT 16.

[g] Kogan, Y. Use-Related Risk Analysis and Comparative Analyses review for RGB-14-P (denosumab) Injection, 60 mg/mL (IND 146025). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);22 MAR 2024. TTT No.: 2023-4930.

[h] Davis. M. HF information Request for "BLA 761439 Human Factors Information Request. Message to Amy Schutte. Silver Spring (MD): FDA, CDER, OSE, RPM (US): 2024 NOV 14.

[i] Re: BLA 761439 Response to Information Request. Cherry Hill (NJ): Hikma Pharmaceuticals USA, Inc. 2024 NOV 18. Available from: \\CDSESUB1\EVSPROD\bla761439\0007\m5\53-clin-stud-rep\535-rep-effic-safety-stud\bone-disease\5354-other-stud-rep\human-factor\other-study-reports-18nov2024.pdf.

- Added section 8.2 patient reminder card.

Based on our independent expert review of the aforementioned information, we determined that these labeling differences in the comparative analyses 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 a CUHF study.

3. CONCLUSION

Based on the aforementioned information, we have determined that the Applicant does not need to submit CUHF study results as part of their marketing application for RGB-14-P (denosumab-xxxx) 60 mg/mL PFS under BLA 761439 to support interchangeability to Prolia PFS. In addition, we maintain or prior determination that the Applicant does not need to submit HF validation study results with their marketing application for RGB-14-P PFS as a proposed biosimilar to Prolia PFS. We have no HF recommendations for this marketing application.

We note that the DMEPA 1 nomenclature and labeling team is evaluating the labels and labeling under a separate cover and based on the outcome of that review, additional labeling comments may be forthcoming.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES

The use-related risk analysis can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761439\0001\m3\32-body-data\32r-reg-info\32r840-risk-management-plan-use-related.pdf

The comparative analysis can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761439\0001\m3\32-body-data\32r-reg-info\32r836-threshold-analyses.pdf

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On November 15, 2024, we issued an information request (IR) requesting the Applicant to specify what changes, if any were made to the URRA, CA, and product user interface since our March 22, 2024, review. On November 18, 2024, the Applicant provided a response that can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761439\0007\m5\53-clin-stud-rep\535-rep-effic-safety-stud\bone-disease\5354-other-stud-rep\human-factor\other-study-reports-18nov2024.pdf

APPENDIX D: LABELS AND LABELING AND PACKAGING

D.1 List of Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[j] along with postmarket medication error experiences with similar products, we reviewed the following RGB-14-P labeling submitted by Hikma Pharmaceuticals, USA, Inc, on September 27, 2024, and November 01, 2024.

Carton labeling and Container label (Image not shown) September 27, 2024	Carton labeling: \\CDSESUB1\EVSPROD\bla761439\0001\m1\us\114-labeling\draft\carton-and-container\1-ml-carton-1pk.pdf Container label: \\CDSESUB1\EVSPROD\bla761439\0001\m1\us\114-labeling\draft\carton-and-container\1ml-syringe.pdf Patient reminder card: \\CDSESUB1\EVSPROD\bla761439\0001\m1\us\114-labeling\draft\carton-and-container\1-ml-reminder-label.pdf
Prescribing Information (Image not shown) November 01, 2024	\\CDSESUB1\EVSPROD\bla761439\0003\m1\us\114-labeling\draft\labeling\1ml-proposed-insert-track-changes-word.docx

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

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/

FLORENCE W MWANGI
03/19/2025 07:28:23 AM

MATTHEW J BARLOW
03/19/2025 07:49:33 AM

ARIANE O CONRAD
03/19/2025 11:01:25 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

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

Date	2/26/2025		
To:	Anita Brown		
Requesting Center/Office	CDER/OPQ	**Clinical Review Division** OPRO/DRBPMII	Other
From	Sangeetha Rajesh OPEQ/OHT3/DHT3C		
Through (Team)	Injection Devices Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Shruti Mistry, Assistant Director OPEQ/OHT3/DHT3C		
Subject	ICCR: 01031370 ICC:2401043 Submission: BLA 761439 Sponsor: HIKMA PHARMACEUTICALS USA INC Drug/Biologic: Denosumab Indications for Use: Prevent skeletal-related events; treat hypercalcemia AND treat osteoporosis; increase bone mass		
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: Our review is focused on the Needle safety feature of the device. The sponsor's Information request responses are adequate and there is no additional information required from the sponsor.		
	PMC/PMR or CR Deficiencies:		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

1. PURPOSE

This review provides an assessment of the needle safety device constituent part[1] 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 essential[2]) treatment that are administered by non-health care professionals.

2. DEVICE DESCRIPTION

Hikma Pharmaceuticals USA, Inc., has submitted an original Biologic License Application (BLA) to seek approval for Denosumab Injection 60mg/1ml single-dose prefilled syringe (RGB-14-P) and Denosumab Injection,120 mg/1.7 mL (70 mg/mL) single-dose vial (RGB-14-X). The reference products that are the basis of this application as defined in the FDA's electronic Purple Book are Prolia® (Denosumab Injection), 60 mg/1 mL single-dose prefilled syringe (PFS) and Xgeva® (Denosumab Injection), 120 mg/1.7 mL (70 mg/mL), both registered by Amgen Inc. and approved under BLA 125320, License 1080. Prolia.

This review is focused on the needle safety feature of the PFS.

The proposed Denosumab Injection, 60 mg/1 mL single-dose prefilled syringe product is a combination product that consists of a drug product component (single use, fix dose) and a device component (a 1mL clear glass syringe supplied with a 27-gauge, ½ inch needle and equipped with a (b) (4) afety needle guard).

RGB-14-P is filled in a 1 mL Type (b) (4) glass syringe with (b) (4) plunger stopper, staked-in needle, and rigid needle shield. The product is assembled into a needle safety device (a single use (b) (4) Needle Guard (b) (4) and (b) (4) plunger rod. Together, these form the single-use device constituent parts of the combination product RGB-14-P prefilled syringe. The needle guard is designed with a robust plunger and built-in extended finger flanges.

Container Closure System (3.2.P.7):

The Letters of Authorization to the referenced DMFs provided in Table 1 below are located in Module 1.4.2 Statement of Right of Reference.

[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, break loose 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.

Table 1. List of Type III and Type V DMFs in support of the primary container closure system components and safety device used with denosumab 60 mg injection

The components and information on the materials used to manufacture each component of the primary packaging and their compendial standards are summarized below in Table 2.

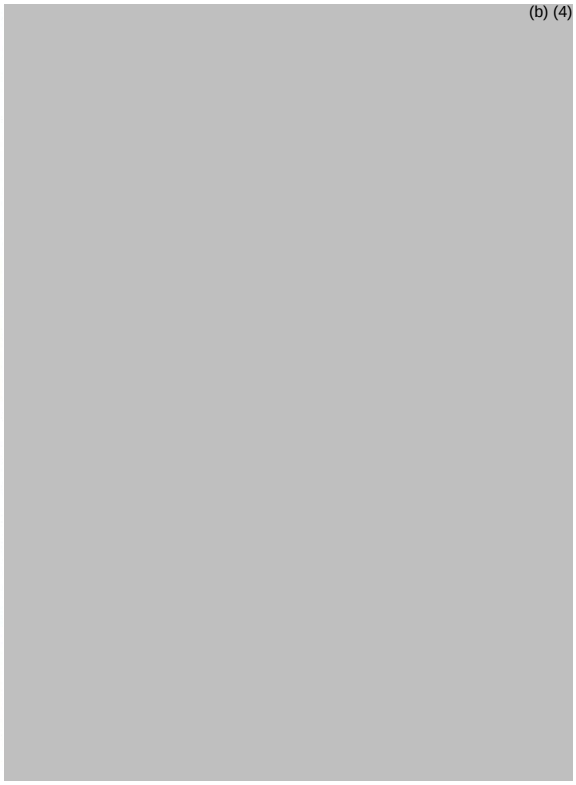
Table 2. Primary container closure components and safety device; a summary of materials and (compendial) standards

Component		Designation	Material	Standard
		(b) (4)		
Syringe barrel		Primary	(b) (4) glass Type (b) (4)	USP <660>, Ph. Eur. 3.2.1
Staked-in-needle		Primary	(b) (4)	Conforms to Section 4 of ISO9626 Standard
Needle shield		Primary (b) (4)	(b) (4)	USP <381>, Ph. Eur. 3.2.9
		Primary		-
(b) (4)		Primary	(b) (4)	USP Class VI
(b) (4)		Primary	(b) (4)	USP, Ph. Eur.
Plunger				
Plunger stopper		Primary	(b) (4)	Sterility: USP <71>, Ph. Eur. 2.6.1 Bacterial endotoxins: USP <85>, Ph. Eur. 2.6.14.
	(b) (4)	***Needle Guard***	(b) (4)	
Body		Safety Device	Plastic (b) (4)	ISO 23908:2011/EN ISO 23908:2013 Annex 1 of Regulation (EU) 2017/745 Guidance for industry and FDA staff: Medical Devices with Sharps Injury Prevention Features (August 9, 2005)
Guard		Safety Device	Plastic (b) (4)	
Spring		Safety Device	Metal (b) (4)	
	Plunger Rod			
Plunger rod		Safety Device	(b) (4)	USP <197>, Ph. Eur. 2.2.24.

Technical drawing of the syringe assembled with the needle safety device is presented in Figure 1.

Figure 1. Technical drawing of the syringe assembled with the needle safety device
1 = needle shield; 2 = plunger rod; 3 = syringe barrel. Measures are in millimeters.

Figure 3. The syringe barrel assembled with a staked needle tip with and without the RNS



Needle Guard:

The needle guard is comprised of a plastic body, plastic guard, and metal spring. This assembly is an anti-needlestick safety device designed to be used with prefilled syringes compliant to ISO Standard 11040-4 with staked needles. Once the pharmaceutical preparation in the prefilled syringe has been delivered, the safety device is automatically activated, and the guard covers the needle when removed from skin.

A photo of the needle guard safety device assembled with the pre-filled syringe is provided in Figure 5. A drawing of the needle guard before and after use is presented in Figure 7.

Figure 5. Photograph of (b) (4) Needle Guard (b) (4) on an Assembled RGB-14-P (b) (4)

Figure 7. Needle guard before and after use

The needle guard complies with ISO Standard 23908. The DP manufacturer's specification is provided in Table 5. For the needle guard manufacturer's specification, refer to Type III DMF # (b) (4)
Certificate of analysis from (b) (4) and supplier's Certificates of Conformance for the needle guard are provided in Annex 3.

Table 5. Specification for (b) (4) Needle Guard (b) (4)

Component	Manufacturer	Composition	Conformity
(b) (4) needle guard	(b) (4)	Body: transparent/colorless (b) (4) Spring: (b) (4)	Based on supplier specification

The certificate of conformance (CoC) for the needle safety device from the supplier, (b) (4) states conformance to specifications and /or drawings in effect for the following characteristics:
-Visual
-Dimensional
-Functional:
Activation force

Separation force
Compression force
Spring force
Syringe Spin
Control Triggering
Pin Gauge

Intended Use:

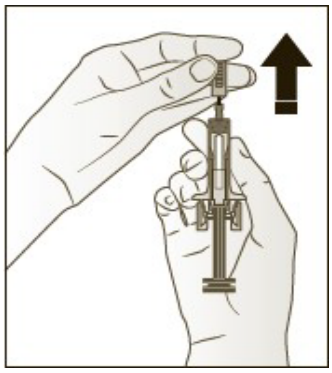
The RGB-14-P is intended for subcutaneous injection in the upper arm, upper thigh, or abdomen., for:

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

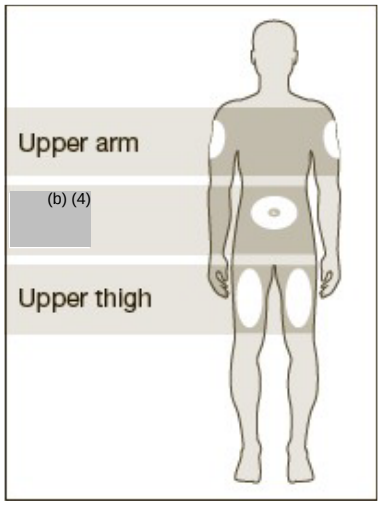
Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	RGB-14-P should be administered by a healthcare professional.
Needle connection (e.g. (b) (4)	Staked
Needle safety type (b) (4)	(b) (4)

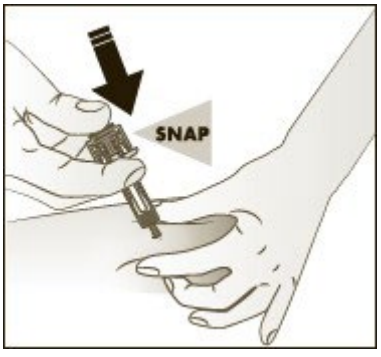
Instructions for use:

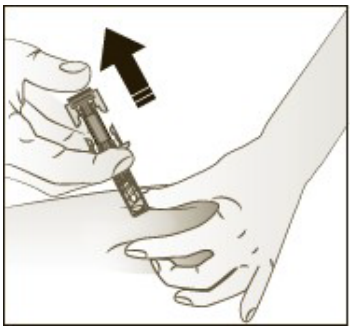
Step 1: Remove Gray Needle Cap

• (b) (4)	 (b) (4)

Step 2: Administer Subcutaneous Injection

• Choose an injection site (**Figure** (b) (4) The recommended injection sites for (b) (4) include: ○ the upper arm or ○ the upper thigh or ○ the abdomen.	 **Figure** (b) (4)

• Insert (b) (4) at a 45-to-90-degree angle (**Figure** (b) (4) **Do not** administer into muscle or blood vessel.	(b) (4) (b) (4)
• Push the plunger with slow and constant pressure all the way down until you feel or hear a „snap” (**Figure** (b) (4) (b) (4)	 **Figure** (b) (4)

• Release the thumb (**Figure** (b) (4) • (b) (4) the syringe safety guard will (b) (4) cover the injection needle.	 **Figure** (b) (4)
• (b) (4) **Do not** put (b) (4) needle cap back on needle.	

Step 3: Dispose of syringe

• Immediately dispose of the syringe and needle cap in the nearest sharps container (b) (4)	(b) (4) (b) (4)
Do not put the needle cap back on the used syringe.	

3. FILING REVIEW (optional)

Checklist	**Present**		
Item	**Yes**	**No**	**N/A**
Device Description	x		
Letters of Authorization	x		
Design Verification Summary and reports for needle safety attributes		x	

4. DEVICE PERFORMANCE REVIEW

Control of drug product (2.3.P.5):
The proposed commercial specifications for *RGB-14-P* are shown below.

Tests	Acceptance criteria		Methods
	At release	End of shelf-life	
Functionality tests			
Break loose force	Less than (b) (4) N		In-house method based on ISO 11040-8 (Force measurement)
Glide force	Less than (b) (4) N		In-house method based on ISO 11040-4 Annex E (Force measurement)
Activation force (safety system)	Less than (b) (4) N		In-house method based on ISO 23908 (Force measurement)
Extractable volume	Not less than 1.0 mL		In-house method based on Ph. Eur (2.9.17) and USP <697> (Weighing)
Lock-out confirmation (safety system visual inspection before and after activation)	Administer the product after confirming that the needle safety device is not activated. The needle safety device must activate immediately after administration and cover the needle completely (access to the needle point is not possible).		In-house method based on ISO 23908 (Visual inspection)
Container closure integrity	No leakage is detected		In-house method based on ASTM F2338-09 (Vacuum decay)
Rigid needle shield removal force	Between (b) (4) N		In-house method based on ISO 11040-4 Annex G.6 (Force measurement)
Challenging the device in safe mode	The needle safety device must remain locked (access to the needle point is not possible) when compressed with (b) (4) N force.		In-house method based on ISO 23908 (Visual inspection)

Functional Performance Tests:
Three Essential Performance Requirements (EPRs) have been identified for the PFS device: EPR-1 Dose Accuracy, EPR-2 Break Loose & Gliding Force, and EPR-3 Safety System. Three additional Primary Functions were identified beyond the EPRs: Primary Function 1 RNS Pull-Out Force, Primary Function 2 NSD Lock-Out Confirmation, and Primary Function 3, Needle Safety Pre-Activation.

EPR-3 is achieved through Design input requirement (DIR-50), Activation Force, which states that "The force to activate the NSD must be ≤ (b) (4) N."

PRIMARY FUNCTION 1 RNS PULL-OUT FORCE

The intent of this Primary Function it to ensure that the RNS can be removed in order to administer the Denosumab 60 mg Injection in Pre-filled Syringe. It is achieved through DIR- 21, RNS Pull-Out Force, which states that "The RNS pull out force must be between (b) (4) N."

PRIMARY FUNCTION 2 NSD LOCK OUT CONFIRMATION

The intent of this Primary Function is to prevent Sharp Injuries. It is achieved through DIR-39, Compression Force NSD, which states that "The force to override the activated locked guard, to the un-activated position must be ≥ (b) (4) N (b) (4) lbs.)."

PRIMARY FUNCTION 3 NEEDLE SAFETY PRE-ACTIVATION

The intent of this Primary Function it to ensure that the needle safety does not activate prior to use. It is achieved through DIR-15, Sharp Injuries Protection, which states that "The DDC must be equipped with a safety feature to protect intended users from sharps injuries."

Design Verification Testing (3.2.R.8.28):

In the Design Verification Plan (DVP) [4] a risk-based methodology was used to determine the confidence level and target reliability (p value). The table below describes the target reliability (p-value), confidence level *k* factor utilized, and acceptance criteria used in each tolerance interval calculation. This calculation determines if the acceptable confidence level of (b) (4) of each DIR has been met.

DIR ID	Design Input Requirements	Risk Level	Target Reliability (p-value)	Confidence Level	*k* factor	Acceptance Criteria
DIR-15	Sharp injuries protection	Medium	(b) (4)		N/A (Attributive Test)	After activation of the device, the distance between the surface of the NSD and the needle tip has to be ≥ (b) (4) mm. Achieved Confidence Level ≥ (b) (4)% 0 failures
DIR-21	RNS pull out force	Medium			Two-sided 2.5549	(b) (4)
DIR-31	CCS sterility	Medium			N/A (Attributive Test)	The syringe container closure system must maintain drug product sterility throughout shelf life Achieved Confidence Level ≥ (b) (4)% 0 failures
DIR-32	Extractable volume	Deliverable volume per ISO 11608-1			Single-sided 2.6083	(b) (4)
DIR-37	Injection force	Medium			Single-sided 2.2198	
DIR-39	Compression force NSD	Medium			N/A (Attributive Test)	At a force of (b) (4) 0N (b) (4) lbs) the activated needle safety guard should not be overridden. Achieved Confidence Level ≥ (b) (4)% 0 failures
DIR-50	Activation force	Medium			Single-sided 2.2198	(b) (4)

* Risk level of "Medium" equates to a probability of (b) (4)% confidence. Nevertheless, sharp-injuries protection will be sampled in accordance with a probability of (b) (4) (b) (4)% confidence, which equals 300 samples for an attribute test, in alignment with ISO 23908 guidance for sharps injury protection.

DIR ID	Design Input Requirements	Risk Level	Sample Configuration	Sample Size	Acceptance Criteria	Test Method
DIR-15	Sharp injuries protection	Medium	DDC	300*	After activation of the device, the distance between the surace of the NSD and the needle tip has to be ≥ (b) (4)nm.	5-01613-E0-04 [5]
DIR-21	RNS pull out force	Medium	DDC	30	The Rigid Needle Shield pull out force must be between (b) (4) (b) (4)N	5-01613-E0-05 [6]
DIR-31	CCS sterility	Medium	DDC	60	The syringe container closure system must maintain drug product sterility throughout shelf life	5-00000-E0-00 [7]
DIR-32	Extractable volume	Deliverable volume per ISO 11608-1	DDC	30	The syringe shall maintain its extractable volume to deliver the labelled dose of 1 mL	5-01613-E0-02 [8]
DIR-37	Injection force	Medium	DDC	30	The break loose and gliding force must be ≤ (b) (4)N.	5-01613-E0-02 [8]
DIR-39	Compression force NSD	Medium	DDC	60	At a force of (b) (4)0N ((b) (4)lbs) the activated needle safety guard should not be overridden.	5-00000-E0-02 [8]
DIR-50	Activation force	Medium	DDC	30	The force to activate the NSD must be ≤ (b) (4)N.	5-01613-E0-02 [8]

* Risk level of "Medium" equates to a probability of (b) (4)% confidence. Nevertheless, sharpinjuries protection will be sampled in accordance with a probability of (b) (4)% confidence,which equals 300 samples for an attribute test, in alignment with ISO 23908 guidance for sharps injury protection.

Design Verification Functional Stability Protocol." Test conditions under evaluation are described in Table 3 below.

Table 3. RGB-14-P Functional Stability Testing Conditions

Description	Temperature [°C]	Humidity [%RH]	Time points tested [months] / [days]
Real Time Aging	5 ± 3	None	0, 3, 6, 9, 12, 18, 24, and 36 months
Accelerated Aging #1	25 ± 2	60 ± 5	0, 1, 3, and 6 months
Accelerated Aging #2	40 ± 2	75 ± 5	0, 30, and 100 days

Results obtained to-date for the DIRs tested under Real Time Aging conditions are presented in Table 4.

Table 4. RGB-14-P DDC Stability Testing at Real Time Aging Conditions

DIR	Reason for inclusion	Time point [months]							
		0	3	6	9	12	18	24	36
DIR-6, Maintain DDC functionality	Overarching requirement for stability study[1]	Pass	Pass	Pass	Future stability time point	Future stability time point	Future stability time point	Future stability time point	Future stability time point
DIR-15, Sharp injuries protection	Functional performance	Pass	Pass	N/T[2]	N/T[2]	N/T[2]	N/T[2]	N/T[2]	N/T[2]
DIR-16, Tamper evident feature	Functional performance	Pass	N/T[3]	Pass	Future stability time point	Future stability time point	Future stability time point	Future stability time point	Future stability time point
DIR-19, DDC Tamper-Evident Seal Opening	Functional performance	Pass	N/T[4]	N/T[4]	Not required[5]	Not required[5]	Not required[5]	Not required[5]	Not required[5]
DIR-21, RNS pull out force	Functional performance	Pass	Pass	Pass	Future stability time point	Future stability time point	Future stability time point	Future stability time point	Future stability time point
DIR-31, CCS sterility	Functional performance	Pass	Pass	Pass	Future stability time point	Future stability time point	Future stability time point	Future stability time point	Future stability time point
DIR-32, Delivered volume	Functional performance, EPR-1	Pass	Pass	Pass	Future stability time point	Future stability time point	Future stability time point	Future stability time point	Future stability time point
DIR 33, Drug compatibility with syringe and plunger stopper	Extractables and Leachables	Pass	N/Av[6]	N/Av[6]	N/Av[6]	N/Av[6]	N/Av[6]	N/Av[6]	N/Av[6]
DIR-35, Shelf life characteristics maintenance	Overarching requirement for stability study[7]	Pass	Pass	Pass	Future stability time point	Future stability time point	Future stability time point	Future stability time point	Future stability time point
DIR-37, Injection (Break Loose) Force	Functional performance, EPR-2	Pass	Pass	Pass	Future stability time point	Future stability time point	Future stability time point	Future stability time point	Future stability time point
DIR-37, Injection (Gliding) Force	Functional performance, EPR-2	Pass	Pass	Pass	Future stability time point	Future stability time point	Future stability time point	Future stability time point	Future stability time point
DIR-39, Compression force NSD	Functional performance	Pass	Pass	Pass	Future stability time point	Future stability time point	Future stability time point	Future stability time point	Future stability time point
DIR-50, Activation Force	Functional performance, EPR-3	Pass	Pass	Pass	Future stability time point	Future stability time point	Future stability time point	Future stability time point	Future stability time point

[1] – The acceptance criteria for DIR-6 are the successful testing of functional performance DIR-21, DIR-31, DIR-32, DIR-37, DIR-39, and DIR-50.
[2] – Testing for DIR-15 was discontinued after the 3-month time point. The DIR states that the DDC must be equipped with a safety feature to protect intended users from sharps injuries. As aging does not affect the presence of the NSD, checking was stopped.
[3] – Testing was inadvertently not performed. However, passing results were obtained at t = 6 months, so there is no risk.
[4] – Testing was inadvertently not performed. However, DIR-16 provides evidence of the tamper-evident seal integrity at t = 6 months, so there is no risk of DIR-19 failure.
[5] – Because DIR-16 verifies the tamper-evident seal integrity, DIR-19 will not be tested at future timepoints.
[6] – DIR-33 will be tested per the drug stability study (according to ICH Q5C), and the results will be referenced within the Functional Stability Testing Report upon completion.
[7] – The acceptance criteria for DIR-35 are the successful testing of DIR-16, DIR-19, DIR-21, DIR-31, DIR-32, DIR-33, DIR-37, and DIR-50.

Results for the DIRs tested under Accelerated Aging #1 conditions (25 ± 2 °C; 60 ± 5 %RH) are presented in Table 5. Results obtained to-date for the DIRs tested under Accelerated Aging #2 conditions (40 ± 2 °C; 75 ± 5%RH) are presented in Table 6.

Table 5. RGB-14-P DDC Stability Testing at Accelerated Aging #1 Conditions

DIR	Reason for inclusion	Time point [months]			
		0	1	3	6
DIR-6, Maintain DDC functionality	Overarching requirement for stability study[1]	Pass	Pass	Pass	Pass
DIR-15, Sharp injuries protection	Functional performance	Pass	Pass	Pass	N/T[2]
DIR-16, Tamper evident feature	Functional performance	Pass	N/T[3]	N/T[3]	Pass
DIR-19, DDC Tamper-Evident Seal Opening	Functional performance	Pass	N/T[4]	N/T[4]	N/T[4]
DIR-21, RNS pull out force	Functional performance	Pass	Pass	Pass	Pass
DIR-31, CCS sterility	Functional performance	Pass	Pass	Pass	Pass
DIR-32, Delivered volume	Functional performance, EPR-1	Pass	Pass	Pass	Pass
DIR-37, Injection (Break Loose) Force	Functional performance, EPR-2	Pass	Pass	Pass	Pass
DIR-37, Injection (Gliding) Force	Functional performance, EPR-2	Pass	Pass	Pass	Pass
DIR-39, Compression force NSD	Functional performance	Pass	Pass	Pass	Pass
DIR-50, Activation Force	Functional performance, EPR-3	Pass	Pass	Pass	Pass

[1] – The acceptance criteria for DIR-6 are the successful testing of functional performance DIR-21, DIR-31, DIR-32, DIR-37, DIR-39, and DIR-50.
[2] – Testing for DIR-15 was discontinued after the 3-month time point.
[3] – Testing was inadvertently not performed. However, passing results were obtained at t = 6 months, so there is no risk.

Table 6. RGB-14-P DDC Stability Testing at Accelerated Aging #2 Conditions

DIR	Reason for inclusion	Time point [days]		
		0	30	100
DIR-15, Sharp injuries protection	Functional performance	Pass	Pass	Pass
DIR-16, Tamper evident feature	Functional performance	Pass	N/T[1]	N/T[1]
DIR-19, DDC Tamper-Evident Seal Opening	Functional performance	Pass	N/T[1]	N/T[1]
DIR-21, RNS pull out force	Functional performance	Pass	Pass	Pass
DIR-32, Delivered volume	Functional performance, EPR-1	Pass	Pass	Fail[2]
DIR-37, Injection (Break Loose) Force	Functional performance, EPR-2	Pass	Pass	Fail[2]
DIR-37, Injection (Gliding) Force	Functional performance, EPR-2	Pass	Pass	Fail[2]
DIR-39, Compression force NSD	Functional performance	Pass	Pass	Pass
DIR-50, Activation Force	Functional performance, EPR-3	Pass	Pass	Fail[2]

[1] – Testing was inadvertently not performed. However, passing results were obtained at the t = 0 months timepoint. Due to the nature of the tamper evident seal, it is not impacted by temperature and time.
[2] – Testing could not be completed for DIR-32, DIR-37, and DIR-50 at 100 days due to a high force observed during injection, resulting in termination of the test.

Reviewer Comments:

- The sponsor has conducted design verification testing with the final finished combination product at initial conditions, after shipping and after shlef-life including accelerated aging studies. The EPRs evaluated for the needle safety feature include NSD activation force, NSD lockout force, and needle safety preactivation which meet their acceptance criteria after shipping and up to the products shelf life. The sponsor has provided the upper and lower limits along with k-value but at (b)(4)% confidence and (b)(4)% reliability. For a device with needle safety feature, our expectation is 99%C and 99%R.

- The sponsor has demonstrated that the (b)(4)mm gap ensures that there is a minimum protective space between the needle tip and safety feature after activation, they have not provided information regarding testing the risk of accidental access to a sharp once in safe mode per Annex B. This functional testing is required to ensure that the device functions properly when subjected to real-world forces (e.g., pressing against the device).

4.1. Performance Data -

Performance Requirement	Specification	Confidence / Reliability	Verification Data Acceptable (Y/N)
Needle Safety Activation force	(b) (4)	(b) (4)	*n=30,* (b) (4) *Y*
Needle safety lockout force/override force/safe mode challenge			n=60, Y
Needle Safety Pre-activation	Pass		Acceptable based on the protective design features and the supplier's simulated study results.
Needle safety Access in safe mode	(b) (4)	*N/A*	*Sphere test Method Described in ISO 23908 Annex B.*

Information Request #	1
Sponsor Response	Provided below
Reviewer Comments	The sponsor's responses are adequate
Response Adequate:	☑ **Yes** ☐ **No, See IR #**

Reviewer Comments:

1. The NSD (b) (4) from (b) (4) has been used in several combination products and (b) (4) has shown that the safety guard is designed to prevent pre-activation based on its operational mechanism has conducted a simulated use study in accordance with ISO 23908 Annex A - Guidance on Simulated User Studies, where they confirmed that the Safety Guard (b) (4) was activated 100% of the time in the intended environment, with no failures recorded.

The sponsor has provided a letter of authorization to reference (b) (4) Drug master file (DMF).
The following Information request (IR) will be sent to the sponsor regarding the sample size and the Sphere test.

Information Request#1:

(b) (4)

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

FDSA BOT1
02/26/2025 04:05:09 PM
bot-userName-FDSABOT1

M E M O R A N D U M

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

DATE: 1/3/2025

TO: Division of General Endocrinology (DGE)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761439

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Inspections and Investigations (OII) conducted an inspection for the site in June 2024. The inspection was conducted under the following submission: BLA 761379.

The following items were discussed with the site:

- There were discrepancies between source data and data submitted to the Agency.
- The site was reminded of the importance of following the study protocol requirements.

After review of the inspection findings and the site's response, OSIS concluded that there were no human subject safety concerns and data from the reviewed study was reliable.

Site

Facility Type	Facility Name	Facility Address
Clinical	CRS Clinical Research Services Mannheim GmbH	Grenadierstrasse 1, Mannheim, Baden-Wurttemberg, Germany

---

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/

WENDY NG
01/03/2025 03:01:47 PM