BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	BLA 351(k)
Application Number	BLA 761439
Received Date	September 27, 2024
BsUFA Goal Date	September 27, 2025
Division/Office	Division of General Endocrinology/Office of Cardiology, Hematology, Endocrinology and Nephrology Division of Oncology 1/ Office of Oncologic Diseases
Review Completion Date	See DARRTS stamped date
Product Code Name	RGB-14 120 mg/1.7 mL in vial (product code: RGB-14-X) 60 mg/1 mL in prefilled syringe (product code: RGB-14-P)
Proposed Nonproprietary Name[1]	denosumab-qbde
Proposed Proprietary Name[1]	Xtrenbo (proposed interchangeable biosimilar to US-Xgeva); Enoby (proposed interchangeable biosimilar to US-Prolia)
Pharmacologic Class	RANK Ligand (RANKL) Inhibitor
Applicant	Hikma Pharmaceuticals USA Inc.
Applicant Proposed Indications	Enoby is a RANK ligand (RANKL) inhibitor indicated for 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. Xtrenbo is a RANK ligand (RANKL) inhibitor indicated 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

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

	where surgical resection is likely to result in severe morbidity. • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.
Recommendation on Regulatory Action	Approval of RGB-14-P as a biosimilar to US-Prolia, and RGB-14-X as a biosimilar to US-Xgeva. Provisional determination that RGB-14-P is interchangeable with US-Prolia, and that RGB-14-X is interchangeable with US-Xgeva. Approval of interchangeability is precluded due to unexpired first interchangeable exclusivity for Jubbonti and Wyost.

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OPQAIII = Office of Product Quality Assessment III
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
RPM = Regulatory Project Manager
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health
CDRH = Center for Devices and Radiological Health
OTBB = Office of Therapeutic Biologics and Biosimilars

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial

OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
U.S.-Prolia	U.S.-licensed Prolia
U.S.-Xgeva	U.S.-licensed Xgeva

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1. Executive Summary

1.1. Product Introduction

Denosumab is a human monoclonal IgG2 antibody that targets the receptor activator of nuclear factor kappa B ligand (i.e., RANKL). It is marketed in the United States under the tradenames Prolia (60 mg/1 mL in a pre-filled syringe [PFS]) and Xgeva (120 mg/1.7 mL or 70 mg/mL in a single-dose vial). The indications and strength of US-licensed Prolia (US-Prolia) are different from the indications and strength of US-licensed Xgeva (US-Xgeva).

The Applicant proposes RGB-14-P and RGB-14-X as interchangeable biosimilar products to US-Prolia and US-Xgeva, respectively, and the proposed proprietary names are Enoby and Xtrenbo, respectively.

The Applicant seeks the same indications for RGB-14-P and RGB-14-X as those which are approved for US-Prolia and US-Xgeva. The strengths, dosage form, route of administration, indications, and dosing regimens for RGB-14-P and RGB-14-X will be the same as those of US-Prolia and US-Xgeva, which are listed below:

Enoby:

- Strength: 60 mg/1 mL
- Dosage form: injection
- Route of administration: subcutaneous
- Dosing regimen: 60 mg administered subcutaneously once every 6 months
- Indications:
    - Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures
    - Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy
    - Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

Xtrenbo:

- Strength: 120 mg/1.7 mL
- Dosage form: injection
- Route of administration: subcutaneous
- Indications and associated dosing regimen:
  - Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors (120 mg injected subcutaneously [SC] every 4 weeks)
  - 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 (120 mg injected SC every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy)
  - Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy (120 mg injected SC every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy).

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable.

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL (receptor activator of the nuclear factor kappa-B ligand), a transmembrane or soluble protein essential for the formation, function, and survival of osteoclast, the cells responsible for bone resorption thereby modulating calcium release from bone.

This BLA contains sufficient data and information to demonstrate that RGB-14 has the same mechanism(s) of action as those of US-Prolia and US-Xgeva. The Applicant performed a comparative analytical assessment between RGB-14-P and US-Prolia, and between RGB-14-X and US Xgeva. The data provided support the conclusion that RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva, respectively.

US-Prolia is licensed in 60 mg/1 mL in a pre-filled syringe (PFS) and US-Xgeva is licensed in 120 mg/1.7 mL or 70 mg/mL in a single-dose vial.

RGB-14-P is proposed as below:

For subcutaneous injection:

- Single-dose prefilled syringe containing 60 mg denosumab-qbde in 1 mL solution.

RGB-14-X is proposed as below:
For subcutaneous injection:

- Single-dose vial containing 120 mg denosumab-qbde in 1.7 mL (70 mg/mL) solution.

RGB-14-P and RGB-14-X have the same route of administration, strengths, and dosage form as those of US-Prolia and US-Xgeva, respectively.

Additionally, the conditions for use for which the Applicant is seeking licensure have been previously approved for US-Prolia and US-Xgeva.

1.4. Inspection of Manufacturing Facilities

An on-site pre-license inspection for the RGB-14 drug substance and drug product manufacturing facilities at Chemical Works of Gedeon Richter Plc Debrecen, Hungary (FEI: 3022999632) was conducted on March 24 – April 4, 2025, and a 7-item Form FDA 483 was issued to the firm at the end of the inspection. The responses to 483 items were reviewed and found satisfactory.

All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional activity.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

Not applicable.

1.6. Biosimilarity and Interchangeability Assessment

Table 1: Summary and Assessment of Biosimilarity and Interchangeability

Comparative Analytical Studies[2]	
Summary of Evidence	• The comparative analytical assessment included comparisons between RGB-14-P and US-Prolia, and between RGB-14-X and US-Xgeva.

[2]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

	• RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva, respectively, notwithstanding minor differences in clinically inactive components. • RGB-14-P and RGB-14-X have the same strengths, dosage form, and route of administration as US-Prolia and US-Xgeva, respectively.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies	
Summary of Evidence	• Pharmacology/Toxicology information was unnecessary to support the demonstration of biosimilarity
Assessment of Residual Uncertainties	• There are no residual uncertainties from nonclinical Pharmacology/Toxicology perspective
Clinical Studies	
Clinical Pharmacology Studies	
Summary of Evidence	• Pharmacokinetic (PK) similarity between RGB-14-X and US-Xgeva was demonstrated in healthy males in Study RGB-14-001 and supports demonstration of no clinically meaningful differences between RGB-14-X and US-Xgeva. • Because of demonstrated analytical similarity between RGB-14 and US-Xgeva and US-Prolia, PK data from Study RGB-14-001 also support the conclusion that RGB-14-P would be expected to have similar PK as US-Prolia. Additionally, comparative PK data generated with the 120 mg/1.7 mL (US-Xgeva) strength are relevant for conclusions about PK similarity for the 60 mg/1 mL (US-Prolia) strength. • The immunogenicity profiles demonstrated in Studies RGB-14-001 (healthy male subjects) and RGB-14-101 (postmenopausal women with osteoporosis) indicate that RGB-14-X and RGB-14-P do not exhibit meaningful differences compared to US-Xgeva and US-Prolia, respectively. This conclusion is supported by the observation of very low and comparable rates of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) across all treatment arms in both studies. No clinically significant impact of ADAs or NAbs was

	observed on the PK, PD, safety, or efficacy of the study drugs. • The data support that RGB-14-X and RGB-14-P demonstrate no clinically meaningful differences from US-Xgeva and US-Prolia, respectively.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical pharmacology perspective.
Additional Clinical Studies	
Summary of Evidence	• The Applicant conducted a randomized, double-blind comparative clinical study (Study RGB-14-101) in 473 post-menopausal women with osteoporosis to compare the PK, pharmacodynamics (PD), efficacy, safety, and immunogenicity of RGB-14-P and US-Prolia. Patients were randomized to receive RGB-14-P or US-Prolia 60 mg injected SC every six months for one year (Main Period). After one year, patients initially assigned to US-Prolia in the Main Period were re-randomized to either continue US-Prolia or transition to RGB-14-P. Patients who received RGB-14-P during the Main Period continued their treatment with RGB-14-P. Patients were followed for six months after the third dose of study drug. • This study demonstrated that RGB-14-P and US-Prolia have similar efficacy with respect to the percent change from baseline in bone mineral density (BMD) for lumbar spine at Week 52. The 90% confidence interval (CI) for the difference in mean change were within the pre-specified equivalence margin of ±1.45%. • The safety profiles of RGB-14-P and US-Prolia were comparable. The adverse events observed were consistent with the known safety profile of denosumab (as labeled in the US-Prolia USPI). There were no meaningful differences in the incidence of specific adverse events between RGB-14-P and US-Prolia, and the small differences in incidences of some of the treatment emergent adverse events (TEAE) that were observed in the RGB-14-P and US-Prolia arms was likely due to chance. • The study also demonstrated similarity of RGB-14-P and US-Prolia with respect to the pharmacokinetics of denosumab, pharmacodynamic effect on biomarkers of bone turnover, and immunogenicity.

Assessment of Residual Uncertainties	• There are no residual uncertainties.
Switching Study	
Summary of Evidence	• FDA determined that a switching study is unnecessary to support a demonstration of interchangeability for RGB-14-P and RGB-14-X. • The Applicant has provided adequate data and information to support a demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of RGB-14-P and US-Prolia, or use of RGB-14-X and US-Xgeva, is not greater than the risk of using US-Prolia or US-Xgeva without such alternation or switch.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Any Given Patient Evaluation	
Summary of Evidence	• The Applicant has provided adequate data and information, including the analytical and clinical data, to support a demonstration that RGB-14-P and RGB-14-X can be expected to produce the same clinical result as US-Prolia and US-Xgeva, respectively, in any given patient.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Extrapolation	
Summary of Evidence	• Division of General Endocrinology (DGE) and the Division of Oncology 1 (DO1) have determined that the Applicant has provided adequate scientific justification and agrees with the Applicant's justification for extrapolation to the other indications listed in the US-Prolia and US-Xgeva USPIs being sought for licensure based on: 1) the mechanism of action of denosumab, 2) the analysis of the known safety and immunogenicity profiles of denosumab across each of the indications being sought, and 3) the assessment of any differences in expected toxicities for each indication. • The data and information submitted by the Applicant, including the justification for extrapolation, supports

	licensure of RGB-14-P and RGB-14-X as interchangeable biosimilar to US-Prolia and US-Xgeva for the following indications for which US-Prolia and US-Xgeva have been previously approved: ○ Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures. ○ Treatment to increase bone mass in men with osteoporosis, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. ○ Treatment of glucocorticoid-induced osteoporosis who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. ○ Treatment to increase bone mass in men at high for fracture receiving androgen deprivation therapy for prostate cancer. ○ Treatment to increase bone mass in women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer ○ 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.
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of RGB-14-P and RGB-14-X as

	interchangeable biosimilars to US-Prolia and US-Xgeva for the above indications.

1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva, respectively, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between RGB-14-P and US-Prolia, or between RGB-14-X and US-Xgeva, in terms of the safety, purity, and potency of the product. The data and information provided by the Applicant are sufficient to demonstrate that RGB-14-P and RGB-14-X can be expected to produce the same clinical result as US- Prolia and US- Xgeva, respectively, in any given patient. The risk in terms of safety or diminished efficacy of alternating or switching between use of RGB-14-P and US-Prolia, or between use of RGB-14-X and US-Xgeva, is not greater than the risk of using US-Prolia or US-Xgeva without alternation or switch. The data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that RGB-14-P and RGB-14-X are biosimilar to US-Prolia and US-Xgeva and meet the statutory criteria to be interchangeable with US-Prolia and US-Xgeva as follows:

- RGB-14-P, 60 mg/mL injection for SC use in a single-dose PFS as an interchangeable biosimilar to US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS,
- RGB-14-X, 120 mg/1.7 mL injection for SC use in a single-dose vial as an interchangeable biosimilar to US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial,

for each of the following indications for which US-Prolia and US-Xgeva have been previously approved and for which the Applicant is seeking licensure of RGB-14-P and RGB-14-X:

US-Prolia:

- Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to

remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

US-Xgeva:

- 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.

FDA has not identified any deficiencies that would justify a complete response action and has provisionally determined that RGB-14-P and RGB-14-X meet the statutory interchangeability criteria for any condition of use as described above. However, pursuant to section 351(k)(6) of the PHS Act, FDA is unable to approve RGB-14-P and RGB-14-X as interchangeable because of unexpired first interchangeable exclusivity (FIE) for US-licensed Jubbonti and Wyost. FDA has previously determined that FIE for Jubbonti and Wyost will expire on October 29, 2025. Refer to the Purple Book at https://purplebooksearch.fda.gov/. Therefore, BLA 761439 will be administratively split to facilitate an approval action for RGB-14-P and RGB-14-X as biosimilar to US-Prolia and US-Xgeva ("Original 1") and a provisional determination that RGB-14-P and RGB-14-X would be interchangeable with US-Prolia and US-Xgeva ("Original 2"), but for unexpired exclusivity.

The review team recommends approval of RGB-14-P and RGB-14-X as biosimilar products as follows:

- RGB-14-P, 60 mg/mL injection for SC use in a single-dose PFS is biosimilar to US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS,
- RGB-14-X, 120 mg/1.7 mL injection for SC use in a single-dose vial is biosimilar to US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial.

The review team also recommends a Provisional Determination that:

- RGB-14-P, 60 mg/mL injection for SC use in a single-dose PFS meets the applicable standards for interchangeability with US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS, and
- RGB-14-X, 120 mg/1.7 mL injection for SC use in a single-dose vial meets the applicable standards for interchangeability with US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial.

BLA 761439/Original 2 will receive a Provisional Determination letter. The Applicant is expected to submit an amendment seeking approval no more than six months prior to the expiration of such exclusivity or when the Applicant believes that BLA 761439 Original 2 will become eligible for approval.

The CDTL and Division Signatory agree with the above assessment and recommendation.

Author:

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Cross Disciplinary Team Leader, DGE

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

On December 20, 2019, an initial advisory meeting was held between FDA and the Applicant. To support a 351(k) application, the Applicant proposed to conduct a comparative pharmacokinetic (PK) study in healthy male volunteers to compare the safety, tolerability, and immunogenicity profiles of RGB-14-P and European Union (EU)-Prolia, and United States (US)-Prolia, and a comparative clinical study in postmenopausal female patients with osteoporosis to compare the efficacy, safety, pharmacodynamics (PD), PK, and immunogenicity of RGB-14-P and US-Prolia. FDA advised the Applicant to enroll males aged 28 to 55 years of age for the PK study to ensure skeletal maturity and females aged 60 to 90 years of age for the comparative clinical study to match the trial population of the reference product.

On April 6, 2021, the Applicant opened IND 146025 by submitting protocol RGB-14-101 for the comparative clinical study in postmenopausal females. Within this submission, the Applicant indicated that the comparative PK study, comparing RGB-14-X to US-Xgeva, was ongoing in Europe. FDA deemed the use of US-Xgeva in the comparative PK study acceptable because analytic comparability between US-Prolia and US-Xgeva had been demonstrated. FDA also considered the comparative clinical study protocol safe to proceed from a clinical protocol standpoint. However, FDA placed the IND on a full clinical hold because the safety and performance of the needle safety device component of the pre-filled syringe device had not been demonstrated as adequate for clinical use.

On August 6, 2021, the Applicant submitted a complete response to the full clinical hold, and the Study RGB-14-101 was subsequently allowed to proceed.

Table 2: Key interactions between FDA and the Applicant

Date	Event	Comments
December 20, 2019	Initial advisory meeting	Discussed product quality, non-clinical, clinical plan for RGB-14.
October 16, 2020	BPD Type 2 Meeting	FDA recommended single transition from US-Prolia to RGB-14-P in a subset of patients as part of an extension to evaluate the safety of the transition.
April 6, 2021	IND 146025 opened	Full clinical hold issued due to issues related to the needle safety device constituent.
August 6, 2021	Applicant submitted Complete Response to the full clinical hold	Full clinical hold was lifted.
July 19, 2023	BPD Type 2 Meeting	Discussed product quality development for RGB-14.
March 22, 2024	BPD Type 4 Meeting	Discussed proposed format and content for the planned 351(k) BLA submission.
August 2, 2024	Advice letter from FDA	FDA communicated that providing two months of post-transition safety data at the time of initial BLA submission is acceptable to assess major immune-related risks from transitioning from US-Prolia to RGB-14.

2.2. Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

No *in vivo* nonclinical studies were submitted for RGB-14. Refer to Table 3 for a list of clinical studies included in this BLA.

Table 3: Relevant Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study					
Study RGB-14-001	EudraCT No. 2020-003953-32	Compare the pharmacokinetics, pharmacodynamics, safety, and	Randomized, double blind, two-arm, single-dose,	Healthy adult male volunteers	RGB-14-X 60mg SC once: 83 volunteers

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
		immunogenicity of RGB-14-X and US-Xgeva	single-center, parallel-group study.		US-Xgeva 60mg SC once: 82 volunteers
Comparative Clinical Study(ies)					
Study RGB-14-101	EudraCT No. 2020-006017-38	Compare the efficacy, safety, immunogenicity, pharmacokinetics and pharmacodynamics of RGB-14-P and US-Prolia	Randomized, multicenter (Bulgaria, Czech Republic, Hungary, Italy, Poland, Spain, Ukraine, United States), double-blind, comparative clinical study involving two treatment periods.	Female with postmenopausal osteoporosis	**Main period** (52 weeks): RGB-14-P 60mg SC once: 242 patients US-Prolia 60mg SC once: 231 patients **Transition** period (26 weeks): RGB-14-P 60mg SC once: 125 patients US-Prolia 60mg SC once: 63 patients

Authors:
Sooyoung Lim, M.D.
Clinical Reviewer, DGE

Shivangi Vachhani, M.D.
Clinical Team Leader, DGE

3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of BLA 761439 for Enoby and Xtrenbo manufactured by Hikma Pharmaceuticals USA, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Enoby and Xtrenbo are well-controlled and lead to products that are safe, pure, and potent. The comparative analytical data support a demonstration that Enoby and Xtrenbo are highly similar to US-licensed Prolia and US-licensed Xgeva, respectively, notwithstanding minor differences in clinically inactive components. It is recommended that these products be approved for human use under conditions specified in the package inserts. Refer to OPQ memo in DARRTS dated September 22, 2025.

3.2. Devices

Enoby is supplied as a drug-device combination product. Each prefilled syringe of Enoby contains 60 mg of RGB-14. Xtrenbo is supplied as a single-dose vial presentation that is not considered a drug-device combination.

3.2.1. Center for Devices and Radiological Health (CDRH)

The Center for Devices and Radiological Health was consulted for review of the device constituent part of the RGB-14 drug-device combination product. The device constituent parts of the RGB-14 combination product consist of a fixed-dose and single use prefilled syringe (PFS) with a needle safety device. The needle safety device uses a single use (b) (4) Needle Guard (b) (4)

The CDRH review team concluded that the device constituent parts of the combination product are acceptable. Refer to the CDRH consult review dated February 26, 2025, in DARRTS for additional details.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

The Division of Medication Error Prevention and Analysis 1 (DMEPA-1) evaluated the Use-Related Risk Analysis (URRA) and comparative analyses (CA) to determine if human factors (HF) validation study results and comparative use human factors (CUHF) study results are needed to support the marketing application for RGB-14-P (Enoby) 60 mg/mL PFS as an interchangeable biosimilar to U.S.-licensed Prolia. The DMEPA-1 review team determined that the Applicant does not need to submit HF validation or CUHF study results to support this marketing application for RGB-14-P (Enoby) 60 mg/mL PFS. DMEPA-1 has no HF recommendations. Refer to the DMEPA-1 review dated March 19, 2025, for additional details.

3.3. Office of Study Integrity and Surveillance (OSIS)

OSIS audits were requested for one bioanalytical site: (b) (4) (b) (4) and three clinical sites: CRS Clinical Research Services Mannheim GmbH, Germany, Parexel Early Phase Clinical Unit, Harrow, United Kingdom, and Nuvisan GmbH, Neu-Ulm, Bavaria, Germany. The inspections were requested because the pharmacokinetic similarity study RGB-14-001 under BLA 761439 was conducted and analyzed at these sites.

OSIS conducted an inspection for (b) (4) for the analytical portion of pharmacokinetic study RGB-14-001. No FDA Form 483 was issued and there were no identified concerns regarding the reliability of audited concentration data from Study RGB-14-001. Refer to OSIS report dated (b) (4) in DARRTS.

OSIS conducted inspections for clincial sites at Parexel Early Phase Clinical Unit and Nuvisan GmbH, Germany for study RGB-14-001 under BLA 761439. FDA Form 483 was issued for destroying the paper code break emergency envelops at Parexel Early Phase Clinical Unit. FDA form 483 was also issued at Nuvisan GmbH for destroing the paper code break emergency envelops and lack of documentation that subjects were supine for five minutes prior to supine blood pressure measurement. However, for both clinical sites, there were no identified concerns regarding reliability of the data or human subject protection for inspected study RGB-14-001. Refer to OSIS reports dated 7/14/2025 and 7/10/2025, respectively. OSIS determined that an inspection was not needed for CRS Clinical Research Services as the Office of Inspection and Investigations (OII) conducted an inspection for this site in June 2024. Refer to OSIS report dated 01/03/2025, in DARRTS.

3.4. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted an inspection of three 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) for the clinical comparative study RGB-14-101.

Based on the overall inspection results of these CIs, CRO, and the regulatory assessments, OSI concluded that Study RGB-14-101 appears to have been conducted adequately and the clinical data submitted by the sponsor appear acceptable in support of the application. Refer to OSI review dated May 7, 2025, in DARRTS for additional details.

Author:

Sooyoung Lim, M.D.
Clinical Reviewer

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

The Applicant did not provide in vivo pharmacology, animal pharmacokinetics or toxicological studies to support the BLA. The Applicant proposed to support the demonstration of biosimilarity of RGB-14-P and RGB-14-X to US-Prolia and US-Xgeva, respectively, based on comparative analytical assessments and clinical studies. In the absence of physicochemical or bioanalytical differences from the reference products, the Agency did not consider an in vivo animal study comparison necessary to show biosimilarity of RGB-14-P and RGB-14-X to US-Prolia and US-Xgeva, respectively (See section 1.6).

The Sponsor provided in vitro nonclinical primary and secondary pharmacology data of RGB-14-P and RGB-14-X. The in vitro primary pharmacology studies included RANKL binding studies as well as functional evaluations of inhibition of RANK/RANKL signaling and the inhibition of osteoclast differentiation. The results showed that the binding and functional activies of RGB-14-P and RGB-14-X were highly similar to the reference products. Secondary pharmacology studies were conducted to evaluate the binding of RGB-14-P and RGB-14-X to Fc (FcγRIIIa, FcγRIIa,FcγRI and FcRn) and C1q receptors as well as associated antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxic (CDC) effects. RGB-14-P and RGB-14-X had low affinities for Fc and C1q receptors and did not activate ADCC or CDC activity, and were highly similar to the reference products. These data were used as part of the comparative analytical assessment, which was assessed by the quality review team (See Product Quality Review).

4.1.1. Nonclinical Residual Uncertainties Assessment

There are no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

RGB-14-P 60 mg/1 mL drug product in pre-filled syringe (PFS) and RGB-14-X 120 mg/1.7 mL drug product in vial are formulated as sterile, preservative free liquid solutions for subcutaneous administration. The compositions of the RGB-14-P and RGB-14-X drug products are similar to their respective US-licensed reference products. The excipients are qualitatively equivalent, with only minor quantitative differences.

RGB-14-P 60 mg/1mL PFS contains 60 mg RGB-14, 4.6% sorbitol, 18 mM (b) (4) 0.01% polysorbate 20, Water for Injection (USP), and sodium hydroxide to a pH of 5.2. Similarly, RGB-14-X 120 mg/1.7 mL vial is composed of 120 mg RGB-14 (70 mg/mL),

4.6% sorbitol, 18 mM (b) (4) 0.01% polysorbate 20, Water for Injection (USP), and sodium hydroxide to a pH of 5.2. Refer to the Applicant's tables below.

Table 4: Composition of RGB-14-X, RGB-14P, US-Xgeva, and US-Prolia.

Components	RGB-14-X (Proposed)	US Xgeva® (Reference)	Function of the ingredient
Denosumab	70.6 mg/mL	70.6 mg/mL	Drug substance
Glacial acetic acid[1]	1.0809 mg/mL	1.0809 mg/mL	(b) (4)
Sodium hydroxide[2]	q.s.	q.s.	
Sorbitol	46 mg/mL	46 mg/mL	
Polysorbate 20	0.10 mg/mL	0.10 mg/mL	
Water for Injections	q.s.	q.s.	
(b) (4)	-	N/A	

(b) (4)

[2]Sodium hydroxide (b) (4) solution (b) (4) can be used for pH adjustment.

(b) (4)

Component	RGB-14-P (Proposed)	US Prolia (Reference)	Function
Denosumab	60 mg/mL	60 mg/mL	Active substance
Glacial acetic acid[1]	18 mM (equal to 1.0809 mg/mL)	(b) (4)	(b) (4)
Sodium hydroxide[2]	q.s.	q.s.	
Sorbitol	46 mg/mL	47 mg/mL	
Polysorbate 20	0.10 mg/mL	0.10 mg/mL	
Water for Injection	q.s.	q.s.	
(b) (4)	-	N/A	

(b) (4)

[2]Sodium hydroxide (b) (4) solution (b) (4) can be used for pH adjustment.

(b) (4)

Source: Applicant Submission

Comments on Excipients

The excipients used in the manufacturing of RGB-14-P 60 mg drug product PFS and RGB-14-X 120 mg drug product vial are qualitatively the same as those in US-Prolia and US-Xgeva. All excipients are compendial grade and are within the ranges that are

found in the inactive ingredients database. There are no nonclinical safety concerns with the drug product composition.

Comments on Impurities of Concern

No impurities of toxicological concern were identified.

Authors:

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Nonclinical Primary Reviewer

David Carlson, PhD
Nonclinical Supervisor

5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Table 5: Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	Pharmacokinetic (PK) similarities between RGB-14-X and US-Xgeva were demonstrated in healthy adult male subjects (Study RGB-14-001). Comparable PK, pharmacodynamics (PD), and immunogenicity between RGB-14-P and US-Prolia were demonstrated in postmenopausal women with osteoporosis (Study RGB-14-101). These results support the demonstration that RGB-14-X and RGB-14-P have no clinically meaningful differences from their respective reference products, US-Xgeva and US-Prolia.
Immunogenicity	The immunogenicity profiles demonstrated in Studies RGB-14-001 (healthy male subjects) and RGB-14-101 (postmenopausal women with osteoporosis) indicate that RGB-14-X and RGB-14-P do not exhibit meaningful differences compared to US-Xgeva and US-Prolia, respectively. This conclusion is supported by the observation of very low and comparable rates of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) across all treatment arms in both studies. No clinically significant impact of ADAs or NAbs was observed on the PK, PD, safety, or efficacy of the

	study drugs. Consequently, these findings further substantiate that RGB-14-X and RGB-14-P demonstrate no clinically meaningful differences from their respective reference products, US-Xgeva and US-Prolia.

The clinical development program comprises two trials:

1. Randomised, double-blind, single, 60 mg fixed dose, parallel comparative pharmacokinetic and pharmacodynamic (Phase I) study of RGB-14-X and US-sourced Xgeva in healthy adult male subjects (Study number: RGB-14-001)
2. Randomised, double-blind, multicenter Phase III study to assess the efficacy and safety of RGB-14-P compared to US-sourced Prolia in women with postmenopausal osteoporosis (Study number: RGB-14-101)

The Clinical Pharmacology review for this BLA primarily focused on the PK similarity study (Study RGB-14-001) in healthy adult subjects for biosimilarity assessment. Additional PD and immunogenicity data from the comparative clinical study (Study RGB-14-101) in postmenopausal osteoporosis patient population were also reviewed.

The pharmacokinetic (PK) similarity between RGB-14-X and US-Xgeva was established in Study RGG-14-001, as the 90% confidence intervals (CIs) for the geometric mean ratios (RGB-14-X / US-Xgeva) of AUC0-inf, AUC0-last, and Cmax were fully encompassed within the FDA's acceptable bioequivalence range of 0.80–1.25 as shown in Table 6.

Table 6. Summary of statistical analyses for assessment of PK similarity (Study RGB-14-001)

	Geometric Mean (95% CI)						
Parameter (unit)	**n**	**RGB-14-X 60 mg**	**n**	**US-sourced Xgeva® 60 mg**	**Geometric Mean Ratio (RGB-14-X/US-sourced Xgeva®)**	**90% CI**	**Inter CV%**
C_{max} (ng/mL)	83	5404.543 (5083.22, 5746.18)	82	5251.195 (4938.00, 5584.25)	1.029	0.96, 1.10	26.2
$AUC_{0\text{-last}}$ (day*ng/mL)	82	286695.501 (270536.63, 303819.52)	81	258324.233 (243709.01, 273815.93)	1.110	1.04, 1.18	24.6
$AUC_{0\text{-inf}}$ (day*ng/mL)	82	286734.377 (270567.94, 303866.75)	81	258382.880 (243759.47, 273883.56)	1.110	1.04, 1.18	24.6

Source: Study RGB-14-001 Clinical Study Report (CSR), table 13, page 97

Pharmacodynamic (PD) similarity was established by comparing PD endpoints (concentration and %CfB) for sCTX between RGB-14-X and US-Xgeva in Study RGB-

14-001, and for sCTX and P1NP between RGB-14-P and US-Prolia in Study RGB-14-101. For more details, refer to section 5.3 (PD assessment).

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical inspection of Study RGB-14-001 at the PD analytical site and identified the issues: non-adherence to established acceptance criteria for quality control samples on certain dates (March 17, 2021, August 24, 2024, September 8, 2022, and September 21, 2022), failure to retain electronic source data for sample analysis, and unreliable concentration values below the limit of quantification (0.05 ng/mL) and unacceptable %Bias of QC samples for June 1, 2022. However, upon recalculation, the %Bias (%inaccuracy) of QCs for the assay on June 1, 2022, was found to be within the acceptance range. Based on OSIS recommendations, the Applicant submitted an updated report on June 5, 2025. Therefore, in this review the PD evaluation for sCTX in Study RGB-14-001 has been considered with caution. Nevertheless, these specific data anomalies have no impact on the clinical pharmacology review decision as the PD analyses are considered as exploratory and thus results are presented only for completeness in our review.

In terms of immunogenicity assessment, the incidences of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) were comparable between RGB-14-X and US-Xgeva, and between RGB-14-P and US-Prolia in Studies RGB-14-001 and RGB-14-101, respectively (refer to Section 5.4.1 for details).

PK similarity between RGB-14-P and US-Prolia was not assessed in Study RGB-14-101 instead PD and immunogenicity assessments were conducted for their proposed product RGB-14-P versus US-Prolia.

In conclusion, the clinical pharmacology data submitted support the demonstration of no clinically meaningful differences between RGB-14-P and US-Prolia, and between RGB-14-X and US-Xgeva. This evidence contributes to the overall totality of evidence supporting the biosimilarity between RGB-14-P and US-Prolia, and between RGB-14-X and US-Xgeva. The Clinical Pharmacology review team recommends approval of BLA 761392.

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

There are no residual uncertainties from the clinical pharmacology perspective.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

Not Applicable.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

To support a demonstration that RGB-14-X and RGB-14-P have no clinically meaningful differences from US-Xgeva and US-Prolia, respectively, the Applicant submitted two clinical studies, RGB-14-001 and RGB-14-101. The Clinical Pharmacology review for

this BLA primarily focused on the PK and immunogenicity in healthy subjects (Study RGB-14-001) and the additional immunogenicity data from the comparative clinical study (Study RGB-14-101) in postmenopausal osteoporotic patient population. The Applicant collected and analyzed PD data in both clinical studies, for which the results have been presented for completeness. These data were only evaluated to ensure the findings did not conflict with any of the results from the primary endpoint results from other assessments considered as part of decision-making as it pertains to the assessment of biosimilarity.

5.3.1. STUDY RGB-14-001

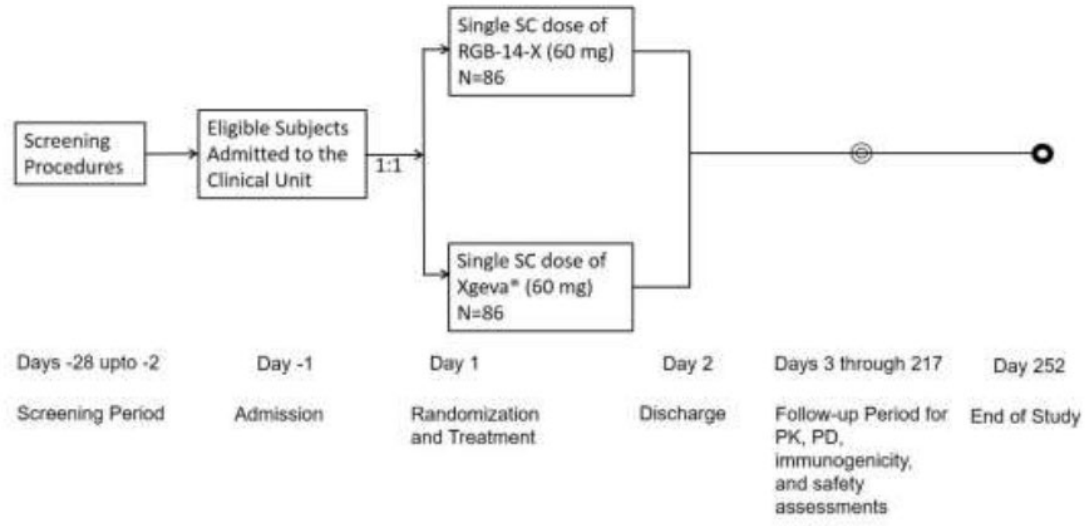
This multicenter, randomized, double-blind "Phase 1" study compared the PK and PD profiles, along with safety, tolerability, and immunogenicity, of a single 60 mg subcutaneous (SC) injection of RGB-14-X versus US-Xgeva in healthy adult male subjects. The primary objective was to characterize and compare the PK profile of RGB-14-X with US-Xgeva following a single 60 mg SC dose.

Clinical Pharmacology Study Design Features

This study included healthy adult male volunteers aged 28-55 years of age with a body weight ≥ 55 and ≤ 90 kg and BMI within the range of 19 to 29 kg/m^2 at the screening and admission. The study design employed a 2-arm, parallel-group methodology, with a planned enrollment of 172 subjects. Subjects were randomly assigned in a 1:1 ratio to receive either the test product (RGB-14-X 60 mg) or the reference product (US-Xgeva 60 mg).

Subjects in both treatment groups received a single SC injection in the abdomen on Day 1 following an overnight fast of at least 8 hours. The study duration encompassed 40 weeks, structured into three phases: screening (up to 28 days), in-house treatment (2 days), and follow-up (250 days). Total subjects confinement was limited to 2 days (from Day -1 morning through Day 2 morning), with the remainder of the study conducted through 25 outpatient visits, concluding with the End-of-Study visit. See Figure 1 for study design.

Figure 1. Study Dosing



Abbreviations: SC: subcutaneous; PD: pharmacodynamic; PK: pharmacokinetic.

Source: Study RGB-14-001 CSR, figure 1, page 33

Clinical Pharmacology Study Endpoints

Primary PK Endpoints:

- Maximum observed serum concentration (Cmax)
- Area under the concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC0-last)
- Area under the concentration-time curve from time 0 extrapolated to infinity (AUC0-inf)

PD Endpoints

- Percent change from baseline (%CfB) in serum carboxyl-terminal telopeptide of type I collagen (sCTX) level
- Area under the effect-time curve (AUEC) of %CfB in sCTX
- Maximum Percent Inhibition (Imax) of sCTX

PK Datasets Analyzed

A total of 165 subjects were randomized in this study, with 83 subjects assigned to the RGB-14-X arm and 82 subjects to the US-Xgeva arm as shown in Table 7. For PK analysis, 165 subjects were included who had at least 1 evaluable PK parameter. Of the three subjects who discontinued the study, two (IDs (b) (6) and (b) (6) withdrew prematurely on Day 28 and Day 62, respectively. The third subjects (ID (b) (6) withdrew at the end-of-study visit on Day 148. None of the discontinuations were attributed to drug-related adverse events. Therefore, all 165 subjects were included for

analysis of Cmax. However, for determination of AUC0-last and AUC0-inf, data from IDs (b) (6) and (b) (6) were excluded due to their early termination.

Table 7. Study subjects included in analysis by treatment and overall

Catagory	RGB-14-X 60 mg (N=83) n (%)	US-Xgeva 60 mg (N=82) n (%)	Overall (N=165) n(%)
Randomized Population	83 (100)	82 (100)	165 (100)
Safety Population	83 (100)	82 (100)	165 (100)
Pharmacokinetic Population	83 (100)	82 (100)	165 (100)
Pharmacodynamic Population	83 (100)	82 (100)	165 (100)
Immunogenicity Populatin	83 (100)	82 (100)	165 (100)

Source: Study RGB-14-001 CSR, table 10, page 72

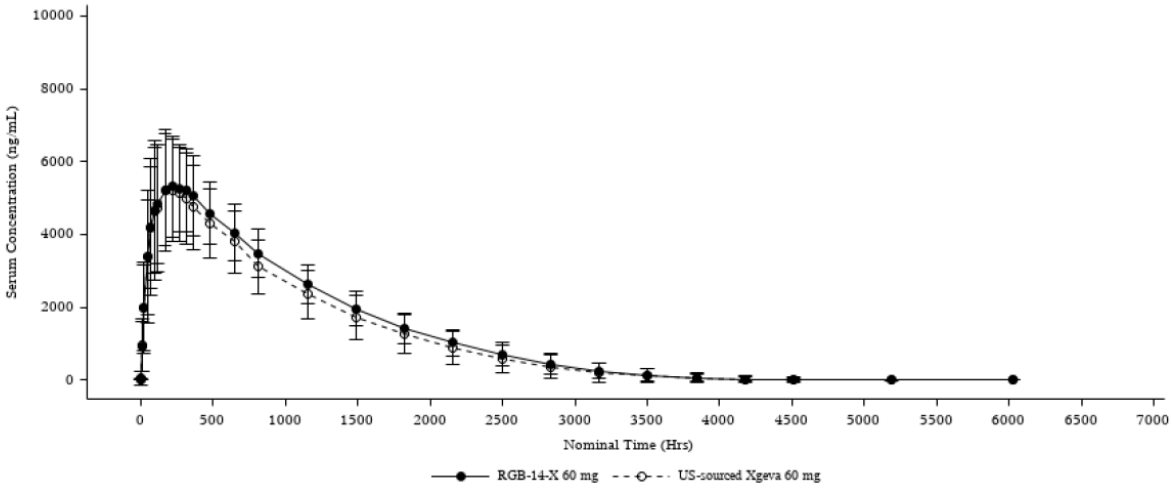
Bioanalytical PK Method and Performance

An electrochemiluminescent (ECL) method was developed and validated to determine serum concentrations of study drug (RGB-14-X, RGB-14-P, US-Xgeva and US-Prolia). This "sandwich" immunoassay uses a MesoScale Discovery (MSD) standard microplate coated with Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL) and blocked with Bovine serum albumin (BSA) buffer. Serum samples are diluted 1:10 in buffer, loaded onto the plate, where study drug binds to immobilized RANKL. After washing, a Sulfo-TAG labelled RANKL detection reagent is added, followed by another wash and addition of a read buffer. Electrochemical stimulation causes photon emission, with the detected counts proportional to bound study drug. Each sample is measured in duplicate wells. The concentration of RGB-14-X/RGB-14-P or US-Xgeva/US-Prolia is calculated using a calibration curve prepared from RGB-14 calibration standard samples. This method enables accurate quantification of study drug in serum samples for both the proposed biosimilar and reference products.

PK Similarity Assessment

The study results showed that the mean study drug serum concentration-time profiles were similar for all treatment groups as indicated in Figure 2**.** Tmax was comparable between RGB-14-X and US-Xgeva (median tmax was 10.931 and 8.972 days for RGB-14-X and US-Xgeva, respectively).

Figure 2. Arithmetic Mean (± SD) serum concentration data versus nominal time by treatment (linear scale; PK population)



Source: Study RGB-14-001 CSR, figure 4, page 79

The geometric mean ratios and the corresponding 90% CIs of RGB-14-X versus US-Xgeva for Cmax, AUC0-last, and AUC0-inf were within the equivalence range of 0.80 to 1.25. See Table 6 for summary of statistical analyses for assessment of PK similarity.

Reviewer Comments:

- *Due to the early termination of subject ID (b) (6) RGB-14-X treatment arm) and (b) (6) (US-Xgeva treatment arm), their PK parameters (AUC values) cannot be calculated reliably. The Applicant excluded the AUC0-last of these two subjects with early termination avoids bias in the PK similarity assessment. The Clinical Pharmacology review team deems the Applicant's exclusion of Subjects (b) (6) and (b) (6) acceptable.*
- *The Applicant's PK analysis is summarized in Table 6. The Clinical Pharmacology review team independently verified the Applicant's findings and confirmed that the analysis meets acceptable standards for demonstrating PK similarity.*

Bioanalytical PD Method and Performance

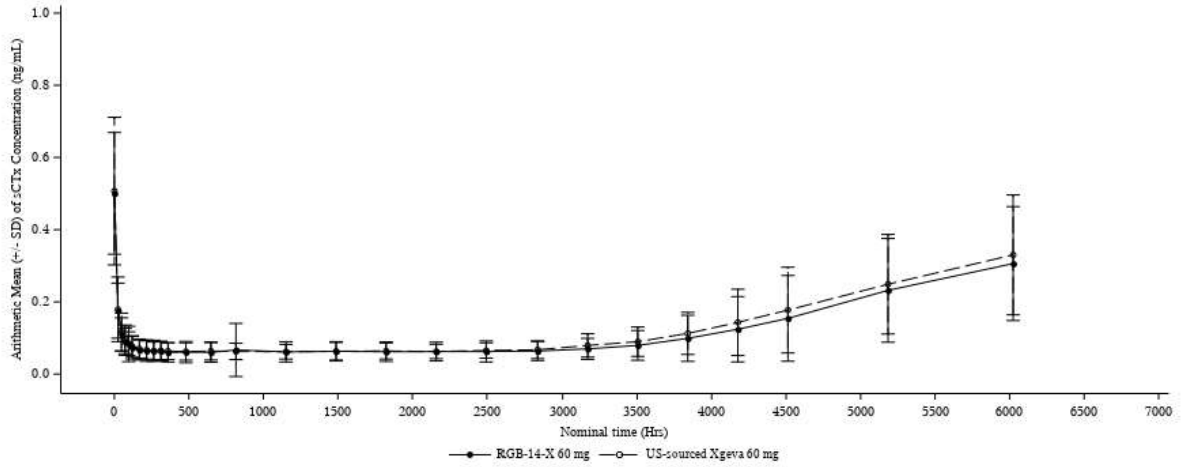
The method for determination of sCTX levels in human serum samples is an electrochemiluminescence (ECLIA) immunoassay-based diagnostic kit from Roche. The Applicant reported that the assay was validated by Roche and its performance was verified at the bioanalytical laboratory in (b) (4)

PD Similarity Assessment

The Applicant collected and analyzed PD data in this study. The results showed that following a single administration of study drug (RGB-14-X and US-Xgeva), for both treatments, sCTX concentrations declined rapidly and re-increased with variable rapidity

starting from around 3500 hours (approximately 146 days). Overall the sCTX concentration time profile showed a comparable concentration-time profile as shown in Figure 3.

Figure 3. Arithmetic Mean (±SD) sCTX Concentration Data vs Nominal Time by Treatment (Linear Scale) (PD Population)



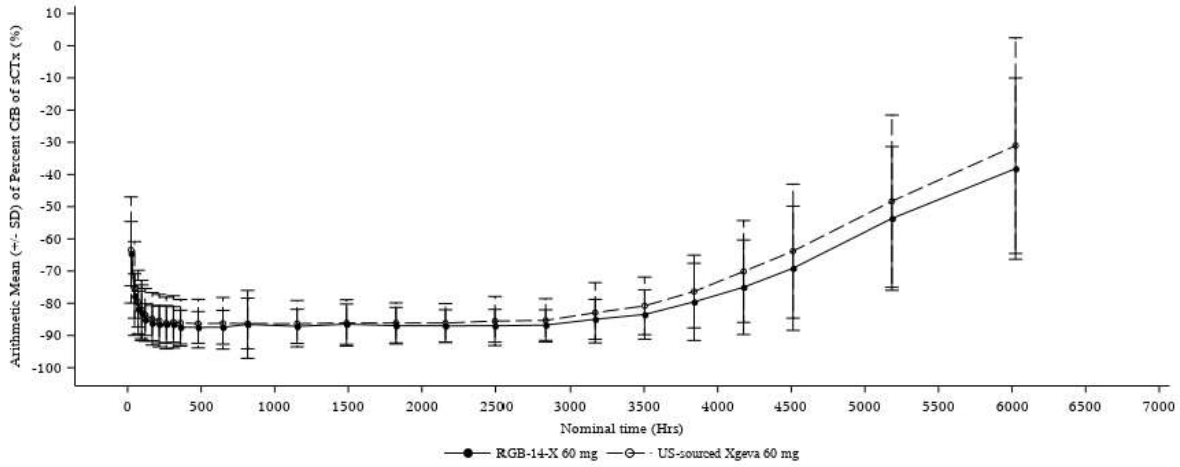
Abbreviations: sCTx = serum carboxyl-terminal telopeptide of type I collagen; SD = standard deviation; US = United States.

Source: Figure 14.2.4.3

Source: Study RGB-14-001 CSR, figure 15, page 101

For the PD parameter in Study RGB-14-001, the arithmetic mean percent change from baseline (%CfB) in serum sCTX concentrations versus nominal time curves on linear scale is presented for pairwise comparisons of all study treatment groups, and PD profiles for sCTX were similar between RGB-14-X and US-Xgeva as shown in Figure 4.

Figure 4. Arithmetic Mean (±SD) sCTX %CfB Data vs Nominal Time by Treatment (Linear Scale) (PD Population)



Change from baseline is calculated as observed - baseline. Percent change from baseline is calculated as 100 x (change from baseline)/baseline.

Abbreviations: sCTx = serum carboxyl-terminal telopeptide of type I collagen; CfB = change from baseline; SD = standard deviation US = United States.

Source: Figure 14.2.4.4

Source: Study RGB-14-001 CSR, figure 16, page 101

Statistical analysis of the estimated PD parameters (AUEC and Imax) of sCTX showed comparable PD parameters values (AUEC and Imax) between the two products with low variability (gCV% <15%) as shown in Table 8.

Table 8. Summary Statistics of PD (sCTX) Parameters by Treatment (PD Population)

Parameter (unit)	Statistics	RGB-14-X 60 mg (N = 83)	US-sourced Xgeva® 60 mg (N = 82)
AUEC (day*%)	n	79	80
	Geometric Mean	19196	18388
	Geometric CV%	10.4	14.6
I_{max} (%)	n	83	82
	Geometric Mean	90.226	89.345
	Geometric CV%	4.7	6.6

n: number of subjects with a specific parameter; N: The number of subjects included in the PD Population for each treatment.

Abbreviations: AUEC = area under the effect-time curve; CV = coefficient of variation; I_{max} = maximum percent inhibition; PD = Pharmacodynamic; sCTx = serum carboxyl-terminal telopeptide of type I collagen; US = United States.

Source: Table 14.2.1.10

Source: Study RGB-14-001 CSR, table 14, page 103

Reviewer comments:

An OSIS inspection was conducted from (b) (4) at (b) (4) for sample analyses performed from 2/16/2021 to 7/13/2023. This bioanalytical laboratory performed the sCTX analysis for Study RGB-14-001. The inspection identified issues with quality control (QC) sample acceptance criteria and data retention practices. Specifically, on four analysis dates (March 17, 2021, August 24, 2022, September 8, 2022, and September 21, 2022), high QC samples exceeded the laboratory's internal acceptance criteria of ± (b) (4)% bias.

Additionally, the laboratory did not retain the raw electrochemiluminescence data from the Cobas 6000 instrument, though they did maintain the final concentration results. Furthermore, some sCTX concentration values were below the validated lower limit of quantitation (0.05 ng/mL), rendering them unreliable.

Given these findings, the PD evaluation for sCTX in Study RGB-14-001 has been considered with caution. Nevertheless, these specific data anomalies have no impact on the clinical pharmacology review decision as the PD analyses are considered as exploratory. The PD results are presented only for completeness in our review.

5.3.2. STUDY RGB-14-101

This is a randomized, double-blind, multicenter “phase 3” study to assess the efficacy and safety of RGB-14-P compared to US-Prolia in women with postmenopausal osteoporosis. The primary objective is to evaluate the similarity of efficacy and pharmacodynamics between RGB-14-P and US-Prolia.

While pharmacokinetic similarity was not assessed as part of the study design, pharmacokinetic samples were collected to determine the study drug concentration to confirm that the immunogenity assays’ drug tolerance was appropriate, and to explore the impact of immunogenicity.

This section discusses the PD similarity between RGB-14-P and US-Prolia. The results related to immunogenicity are discussed in section 5.4.

Clinical Pharmacology Study Design Features

Refer to Sections 6.2. for more detailed information on the design of the study.

Clinical Pharmacology Study Endpoints

Primary PD Enpoint

- AUEC of %CfB sCTX0-m6 until Week 26 to demonstrate the similar PD of RGB-14-P with US-Prolia in female patients with postmenopausal osteoporosis.

PD Datasets Analyzed

Overall, 473 patinets were randomised (242 patients in the RGB-14-P treatment group and 231 in the Prolia treatment group).

Bioanalytical PD Method and Performance

Refer to section 5.3.1. Bioanalytical PD Method and Performance for high level summary for the method description for determination of sCTx levels in human serum samples.

PD Similarity Assessment

AUEC of Percent Change from Baseline in sCTX(0-m6) Concentration Until Week 26

The study results for sCTx %CfB AUEC is shown in Table 9. The study results showed that the difference between treatment groups was not statistically significant (p=0.494) and the PD equivalence was concluded as the 95% CI of the treatment GMR was contained within the 80% to 125% equivalence margin.

Table 9. Analysis of sCTX %CfB AUEC (0 m6) (Pharmacodynamic Analysis Set for Main Period)

		Comparison between Study Treatment Groups	
Study Treatment	Geometric Mean (95% CI)	Geometric Mean Ratio (95% CI)	P-value
RGB-14-P (N=241)	13501.30 (12737.814, 14264.794)	1.01 (0.978, 1.046)	0.494
Prolia (N=229)	13344.65 (12583.291, 14106.002)		

Source: Study RGB-14-101, CSR, table 11-29, page 171

The Applicant reported that following the Week 52 unblinding, it was confirmed that three patients (RGB-14-P: 1 patients and Prolia: 2 patients) presented with sCTX AUEC values less than 0. Due to this they were excluded from the originally planned analyses because the logarithm of a negative value cannot be taken. In light of this, a supplemental analysis was performed. The supplementary analysis of the AUEC of %CfB in sCTX concentration showed the estimated difference in adjusted means between the RGB-14-P and US-Prolia treatment groups was 455.53 (95% CI [−538.170, 1449.228]) and the difference between the treatment groups was not statistically significant (p=0.368).

Overall, the study results showed that the AUEC0-m6 in %CfB in sCTX was comparable between the RGB-14-P and US-Prolia treatment groups.

5.4. Clinical Immunogenicity Studies

The clinical development program for RGB-14 encompassed two key studies, RGB-14-001 and RGB-14-101. Both of which included comparative immunogenicity assessments (detection of Anti-Drug Antibody (ADA) and neutralizing Antibody (NAb)) of the biosimilar candidates against their respective reference products.

5.4.1. STUDIES RGB-14-001 and RGB-14-101

In study RGB-14-001, there was no anti-drug antibody (ADA) and neutralize antibody (NAb) detected from study samples. In study RGB-14-101, no clinically meaningful differences in immunogenicity were observed between the two treatment groups during the main period. Anti-drug antibody (ADA) and neutralizing antibody (NAb) positivity rates remained below 1.0% at all time points. Specifically, the overall incidence of ADA-positive patients was 0.8% (2/239) in the RGB-14-P group and 0.4% (1/228) in the US-Prolia group. Similarly, the overall incidence of NAb-positive patients was 0.4% in both treatment groups (RGB-14-P group: 1/239; US-Prolia group: 1/228). See the sections below for more study design feature and results.

Design features of the clinical immunogenicity assessment

In Study RGB-14-001, 83 subjects receiving RGB-14-X and 82 subjects receiving US-Xgeva were monitored for ADA and NAb evaluation for 252 days following initial dose administration. Similarly, in Study RGB-14-101, 239 subjects receiving RGB-14-P and 228 subjects receiving US-Prolia underwent ADA and NAb evaluation during the main treatment period of 52 weeks and the subsequent 26-week follow-up period.

Refer to Sections 5.3.1 and 6.2 for more detailed study information on the design of the study.

Immunogenicity endpoints

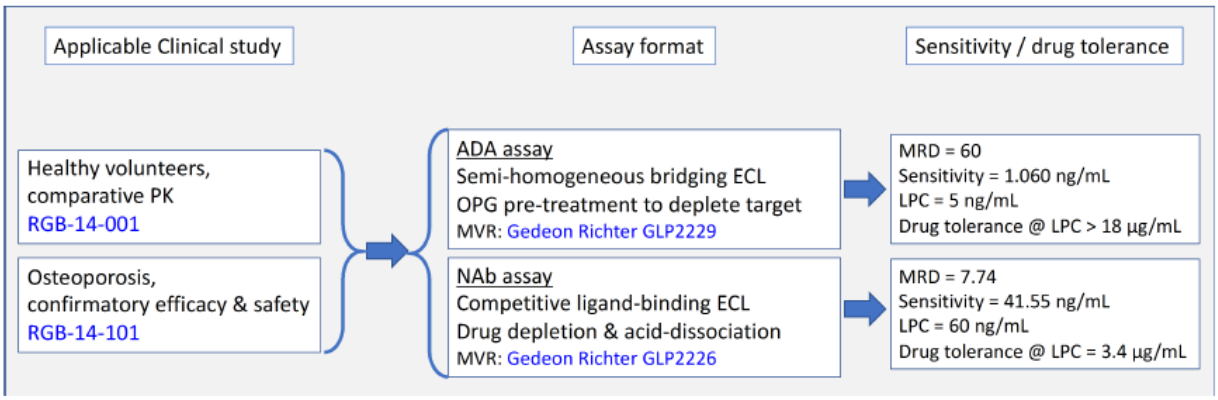
Immunogenicity assessment was proposed as the secondary study endpoints in the following studies:

- Study RGB-14-001:
  - Formation of binding and neutralizing anti-denosumab antibodies
  - Titer of binding anti-denosumab antibodies
- Study RGB-14-101: Immunogenicity
  - Incidence of binding ADAs and NAbs
  - Titre determination of binding ADAs

Immunogenicity assay's capability of detecting the ADA and NAb in the presence of proposed product, U.S.-licensed reference product, and non-U.S.-licensed comparator product (as applicable) in the study samples

The bioanalytical methods described in Figure 5 were employed across RGB-14 clinical studies to systematically monitor ADA and NAb. These methods were methodically developed to ensure appropriate sensitivity levels while maintaining target and drug tolerance requirements.

Figure 5. Overview of the bioanalytical methos applied in RGB-14 clinical studies to monitor ADA and nAb.

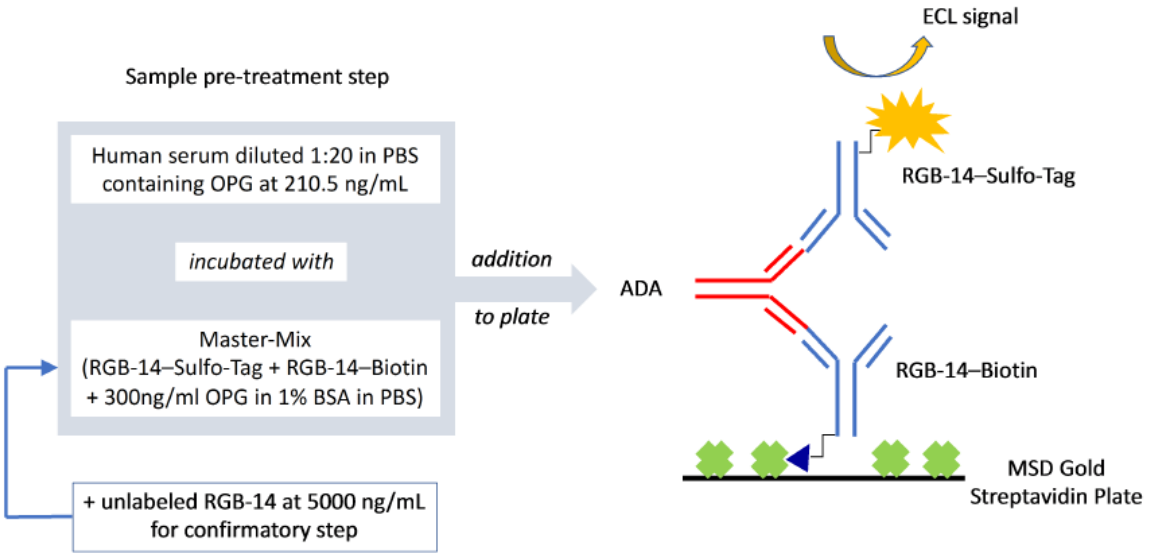


Abbreviations: ADA=anti-drug antibody; ECL=electrochemiluminescent; LPC=low positive control; MRD=minimum required dilution; MVR=method validation report; NAb=neutralizing antibody; OPG=osteoprotegerin; PK=pharmacokinetic

Source: Applicant's submitted integrated summary of immunogenicity, figure 12

The semi-homogeneous bridging immunoassay format illustrated in Figure 6 was developed for detection (screening), confirmation and titration of anti-denosumab (anti-RGB-14, anti- Xgeva and anti-Prolia) antibodies in human serum.

Figure 6. Format of anti-denosumab ADA assay

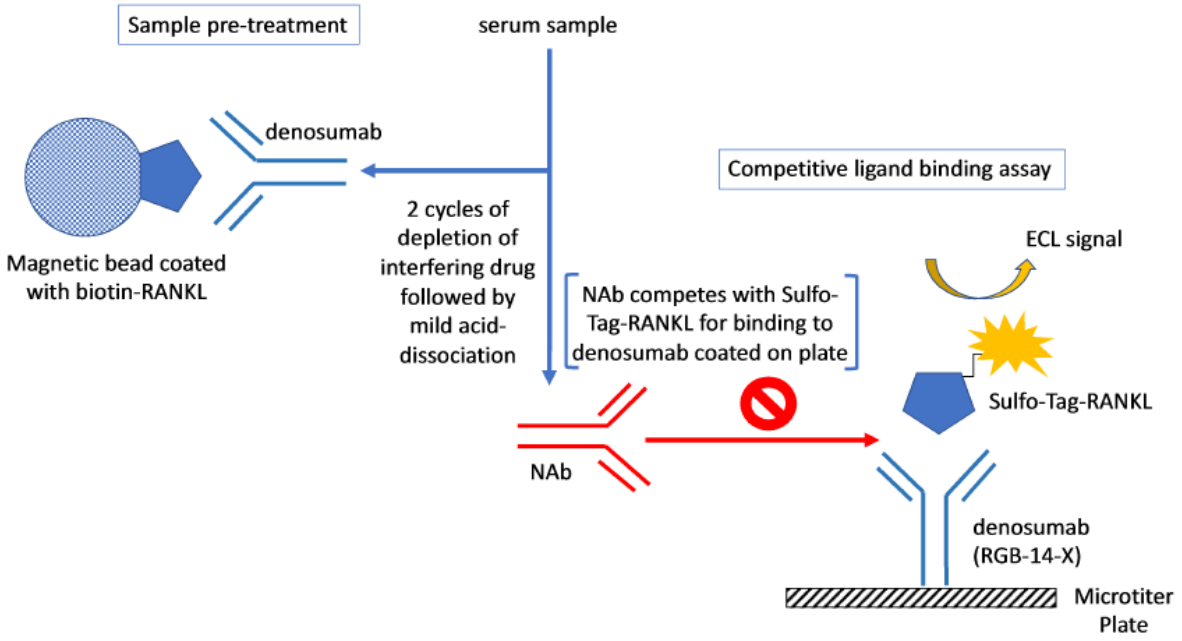


Abbreviations: ADA=anti-drug antibody; BSA=bovine serum albumin; ECL=electrochemilumnescent; MSD=Mesoscale Discovery; OPG=osteoprotegerin; PBS=phosphate-buffered saline

Source: Applicant's submitted integrated summary of immunogenicity, figure 14

A competitive ligand binding assay format used to detect NAb in clinical samples is shown schematically in Figure 7**.**

Figure 7. Nab assay format



Abbreviations: ECL=electrochemiluminescent; NAb=neutralizing antibody; RANKL= receptor activator of nuclear factor kappa-B ligand

Source: Applicant's submitted integrated summary of immunogenicity, figure 21

Refer to OPQAIII review for an assessment of bioanalytical method validation and performance of the ADAs/NAbs assays.

Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation

In Study RGB-14-001, blood samples were collected for immunogenicity evaluation at pre-dose, weeks 2, 4, 9, 17, 21, 25, 31, and 36 (end of study [EOS]). In Study RGB-14-101, blood samples were collected for immunogenicity assessment at pre-dose and Weeks 2, 4, 26, 28, 30, 52, 54, 56, and 78. The immunogenicity sampling schedules in Studies RGB-14-001 and RGB-14-101 are appropriate, as they include baseline (pre-dose) and multiple post-dose timepoints that extend beyond five half-lives of study drug. This comprehensive sampling strategy enables thorough evaluation of immunogenic response over time.

In addition, the study design includes concurrent measurement of drug concentration at the same timepoints as immunogenicity sample collection, allowing parallel assessment of drug levels and antidrug antibody (ADA) emergence. This approach enhances the ability to interpret immunogenicity data within the context of drug exposure.

The inclusion of baseline samples, multiple post-dose timepoints, and corresponding drug concentration measurements provides a robust framework for evaluating the immunogenicity profile of the study drug.

Incidence of ADA and NAb (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study)

The ADA/NAb testing results from Study RGB-14-001 are presented in Table 10. None of subjects in either treatment group showed ADA positivity at any timepoint after receiving a single 60 mg subcutaneous dose of either RGB-14-X or US-Xgeva.

Table 10. Number and percentage of patients with ADA / NAb in study RGB-14-001

Statistic	RGB-14-X (N = 83)		Xgeva (N = 82)	
	Patient n	Patient %	Patient n	Patient %
Pre-dose				
Patients with ADA result	83	100.0	82	100.0
ADA Positive	0	0	0	0
ADA Negative	83	100.0	82	100.0
Missing	0	0	0	0
Patients with NAb result	0	0	0	0
NAb positive	0	0	0	0
Post-dose up to Day 252				
Patients with result	83	100.0	82	100.0
Positive ≥ 1 time-point up to Day 252	0	0	0	0
Negative	83	100.0	82	100.0
Missing	0	0	0	0
Patients with NAb result	0	0	0	0
NAb positive	0	0	0	0

N = total number of subjects in analysis set and treatment group; n = number of subjects within the specified category; ADA = anti-drug antibody; NAb = Neutralising antibody
Source: Table 14.3.8.1 to Table 14.3.8.5, Listing 16.2.9.5 and Listing 16.2.9.6 in CSR for Study RGB-14-001

Source: Integrated summary of immunogenicity, table 46, page 90

The ADA/Nab testing results from Study RGB-14-101 are presented for main treatment in Table 11.

Table 11. Antibodies to Denosumab (ADA) and Neutralising Antibodies (NAbs) Overall Incidence - Main Period

Statistic	RGB-14-P (N = 239)		Prolia (N = 228)	
	Patient n	Patient %	Patient n	Patient %
Pre-treatment (baseline)				
Patients with ADA result	239	100.0	228	100.0
ADA Positive	0	-	1	0.4
ADA Negative	239	100.0	227	99.6
Missing	0	-	0	-
NAb Positive	0	-	0	-
NAb Negative	0	-	1	0.4
Post-dose: Week 2 to Week 52				
Patients with result	239	100.0	228	100.0
ADA Positive ≥ 1 time-point up to Week 52	2	0.8	1	0.4
ADA Negative	237	99.2	227	99.6
Missing	0	-	0	-
NAb Positive ≥ 1 time-point up to Week 52	1	0.4	1	0.4
NAb Negative	1	0.4	0	0

n = number of subjects within the specified category or total number of subjects pre-dose/ post-dose
*% = (number of subjects within the specified category / total number of subjects pre-dose/ post-dose)*100*
N = total number of patients in analysis set and treatment group
ADA = anti-drug antibody; NAb = neutralizing antibody
Source: Table 2.1.1 and Table 2.1.2 in ISI Tables for Study RGB-14-101

Source: Integrated summary of immunogenicity, table 33, page 70

In the main study period from Week 0 to Week 52, 2 out of 239 (0.8%) subjects treated with RGB-14-P and 1 out of 228 (0.4%) subjects in the US-Prolia treatment group had treatment emergent ADA, with an overall incidence of ADA and NAb positivity of <1% at all time points

Following re-randomization and treatment transition at Week 52, only one subject in the US-Prolia/ US-Prolia group had a positive ADA result; no subjects in either the RGB-14-P/RGB-14-P or the US-Prolia/RGB-14-P groups had a positive ADA result from Week 52 to Week 78 (Table 12).

Table 12. Antibodies to Denosumab (ADA) and Neutralizing Antibodies (NAbs) Overall Incidence - Transition Period

Statistic	RGB-14-P/ RGB-14-P (N = 63)		Prolia/Prolia (N = 62)		Prolia/RGB-14-P (N=62)	
	Patient n	Patient %	Patient n	Patient %	Patient n	Patient %
Week 52 (baseline for transition period)						
Patients with ADA result	63	100.0	61	100.0	62	100.0
ADA Positive	0	-	0	-	0	-
ADA Negative	63	100.0	61	100.00	62	100.0
Missing	0	-	1	-	0	-
NAb Positive	0	-	0	-	0	-
NAb Negative	0	-	0	-	0	-
Week 54 to Week 78 (post-re-randomization/transition)						
Patients with result	63	100.0	62	100.0	62	100.0
ADA Positive ≥ 1 time-point up to Wk 78	0	-	1	1.6	0	-
ADA Negative	63	100.0	61	98.4	62	100.0
Missing	0	-	0	-	0	-
NAb Positive ≥ 1 time-point up to Wk 78	0	-	1	1.6	0	-
NAb Negative	0	-	0	-	0	-

n = number of subjects within the specified category or total number of subjects pre-dose/ post-dose
*% = (number of subjects within the specified category / total number of subjects pre-dose/ post-dose)*100;*
N = total number of patients in analysis set and treatment group; ADA = anti-drug antibody; NAb = neutralizing antibody
Source: Table 2.1.1.2 and Table 2.1.2.2 in ISI Tables for Study RGB-14-101

Source: Integrated summary of immunogenicity, table 35

Reviewer comments:

The was no ADA or NAb detected in the study sample from the Study RGB-14-001.

The overall incidence of ADA and NAb during the Main Treatment Period was less than 1%, observed in Study RGB-14-101. In the Transition Period, 1.6% ADA and NAb positivity was observed, but this incidence was observed in the US-Prolia to US-Prolia transitioning group. No incidence was observed in the RGB-14-P to RGB-14-P group or the US-Prolia to RGB-14-P treatment group. The results indicated that switching between RGB-14-P and US-Prolia did not lead to ADA or NAb development in the intended patiend population..

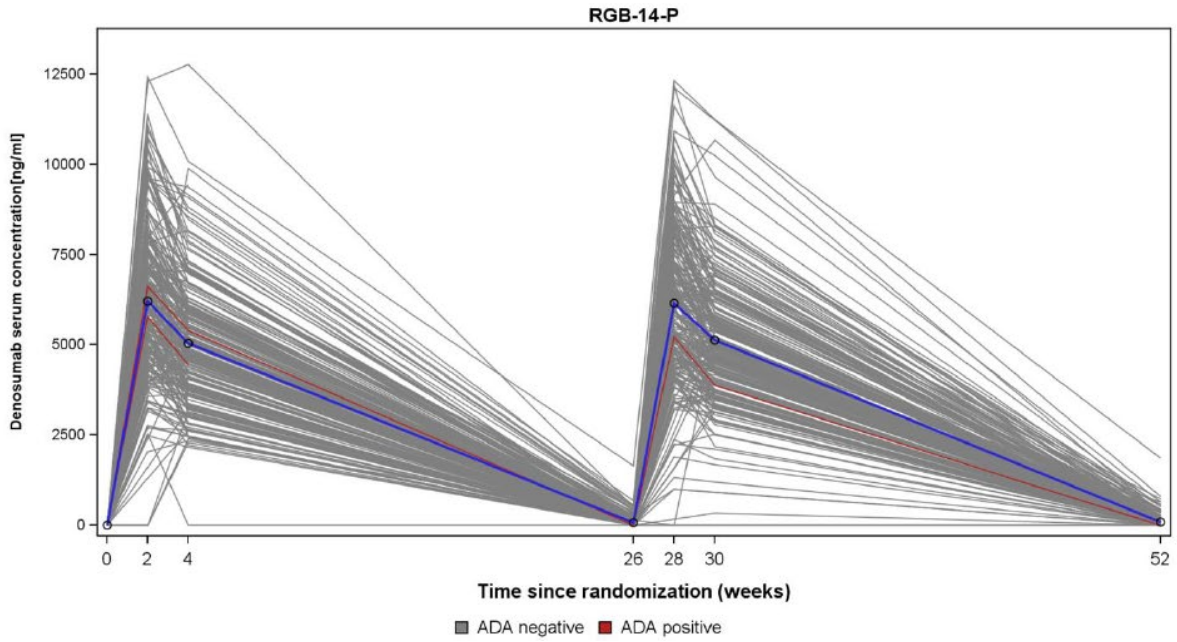
Clinical pharmacology review team has verified and confirmed these study analyses.

Impact of ADA and NAb on the PK, PD, safety, and clinical outcomes of the proposed product

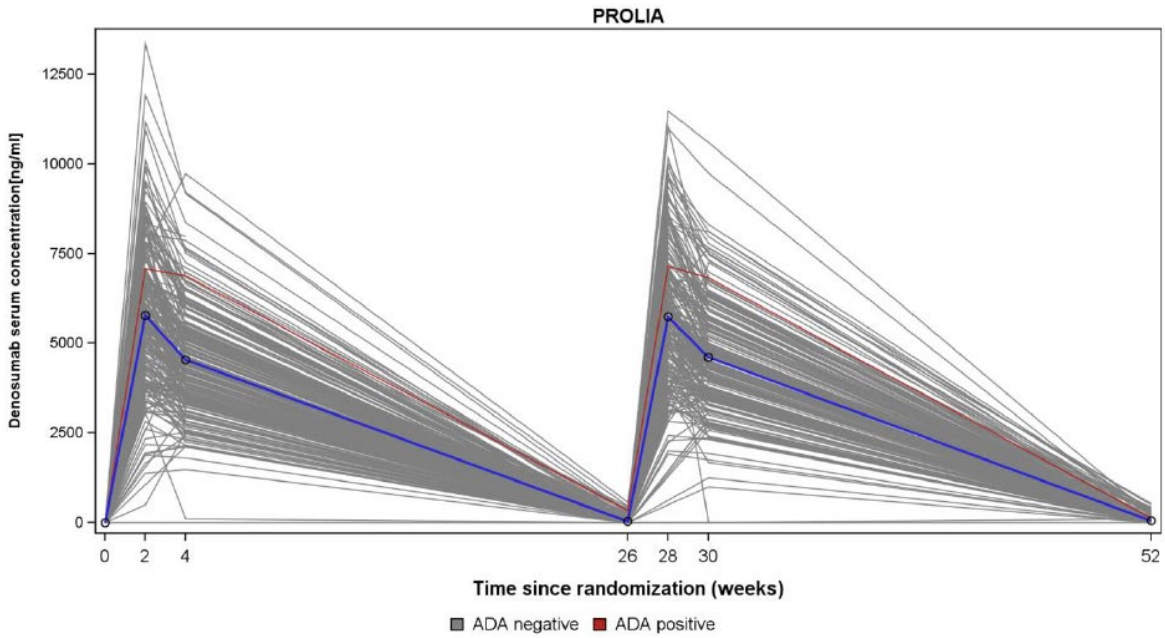
Study RGB-14-101 showed that neither the two RGB-14-P-treated subjects nor the single US-Prolia-treated subject with ADA signals during the main study period from Week 0 to Week 52 had diminished exposure compared to mean exposure value of ADA negative subjects as shown in Figure 8.

Figure 8. Serum study drug concentration vs time by ADA status from week 0 to week 52 (main treatment period) of Study RGB-14-101

a) RGB-14-P treatment group



b) Prolia treatment group



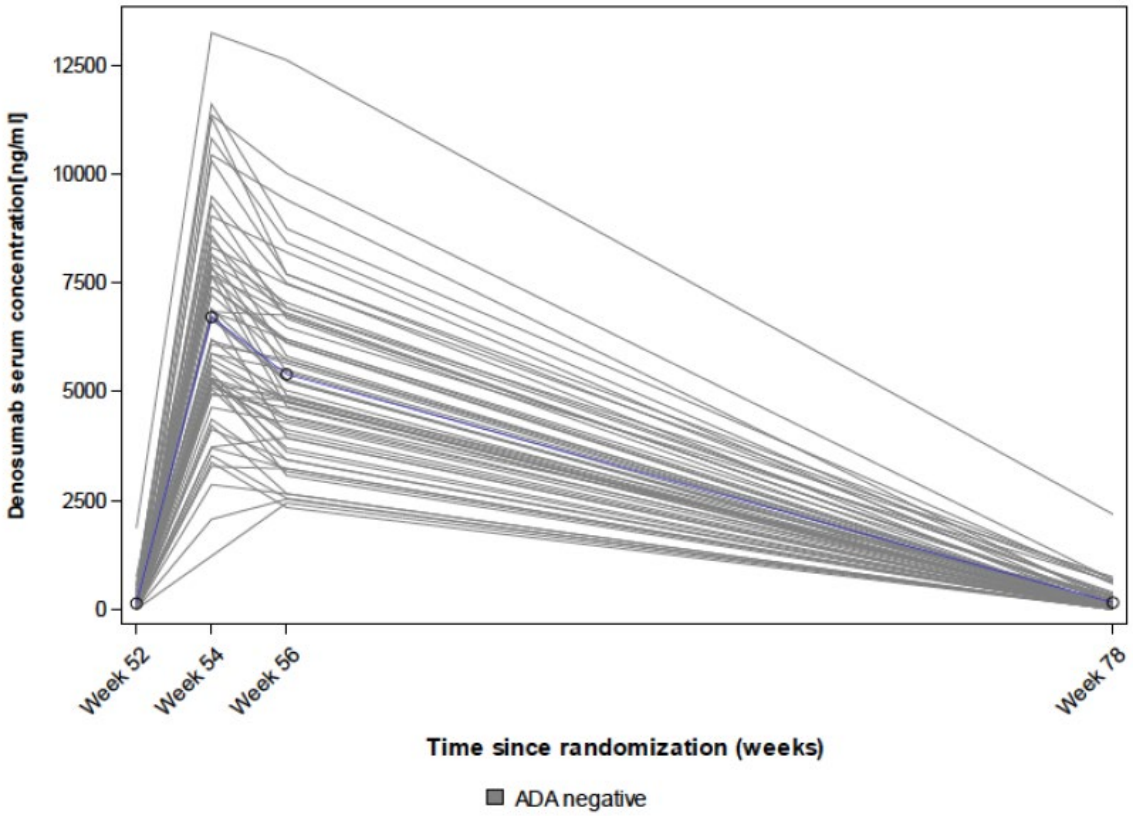
ADA = anti-drug antibody
Mean value for ADA negative subpopulation is displayed in blue.
Source: Figure 2.2.3.1 in ISI Tables for Study RGB-14-101

Source: Integrated summary of immunogenicity figure 33, page 77

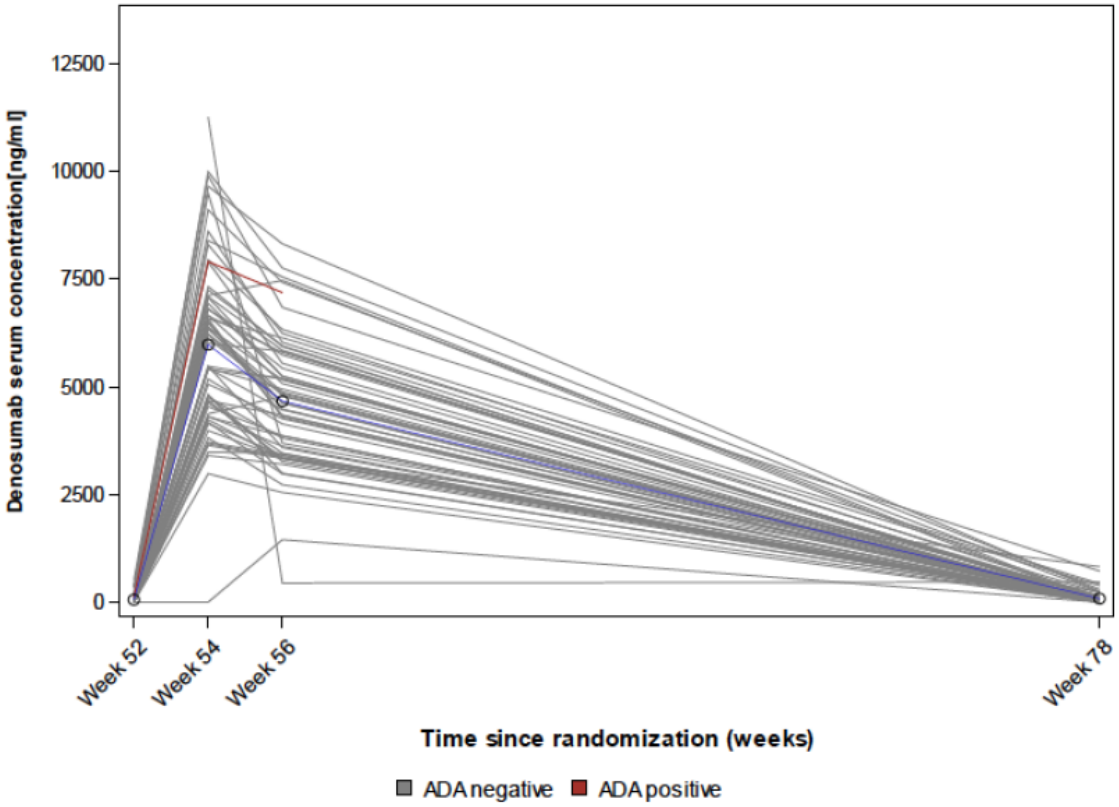
In case of transitioning period from week 52 to week 78, the single US-Prolia-treated subject assigned to the Prolia/Prolia group, who tested positive for ADA also maintained comparable exposure levels as compared to mean exposure value of the ADA negative subjects as shown in Figure 9

Figure 9. Serum study drug concentration vs time by ADA status from week 52 to week 78 of Study RGB-14-101

a) RGB-14-P / RGB-14-P treatment group



b) Prolia / Prolia treatment group



ADA = anti-drug antibody
Mean value for ADA negative subpopulation is displayed in blue.
Source: Figure 2.2.3.2 in ISI Tables for Study RGB-14-101

Source: Integrated summary of immunogenicity, figure 34, page 78

Reviewer's comments:

The observed incidence of ADA and NAb in the Study RGB-14-101 (refer to Table 11 and Table 12) did not have any impact on the study drug concentration. Clinical pharmacology review team has verified and confirmed these study analyses.

Impact of ADA and Nab on Efficacy

The impact of ADAs on efficacy was evaluated by comparing change from baseline in LS BMD at Week 52 per treatment group and ADA status (i.e., subjects with at least one ADA-positive sample up to Week 52 and ADA-negative subjects) in the Main Period of Study RGB-14-101. While the small proportion of patients in either treatment group that were positive for ADAs is reassuring, it precludes a meaningful comparative assessment of the impact of immunogenicity on efficacy. However, the available data do not suggest that ADAs result in decreased efficacy in RGB-14-P group (Table 13).

Table 13: Analysis impact of ADA status on percent change from baseline in lumbar spine BMD at Week 52, Immunogenicity Analysis Set, Study RGB-14-101, Main Period

	RGB-14-P (N=239)		US-Prolia (N=228)	
	ADA positive N=2	ADA negative N=237	ADA positive N=1	ADA negative N=227
LS mean percent change from baseline to Week 52 lumbar spine BMD (95% CI)	8.38 (-)	5.66 (5.19-6.13)	1.17 (-)	5.21 (4.64-5.78)

Source: Module 5.3.5.3. Integrated Summary of Immunogenicity, Table 40, page 81

Impact of ADA and Nab on Safety

As discussed in Section 6.3.3, the clinical reviewer searched the safety dataset for AEs related to anaphylaxis and hypersensitivity.

In Study RGB-14-101, there were no events of anaphylaxis in any treatment group. No patient in any group or period who reported adverse events related to hypersensitivity ever tested positive for post-treatment ADAs. The ADA-positive patients in this study did not report adverse events that would likely be related to immunogenicity.

Therefore, the results do not indicate that the immunogenicity had an effect on the safety of RGB-14-P, including patients who underwent the transition from US-Prolia to RGB-14-P.

In conclusion, the approach to demonstrate the impact of ADAs and NAbs on the PK, safety, and clinical outcomes appears reasonable. There was no evidence of meaningful influence of ADAs or NAbs on the PK, safety, or clinical outcomes between the studied products.

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

The Applicant conducted a single comparative clinical study comparing the efficacy and safety of RGB-14-P and US-Prolia in postmenopausal women with osteoporosis (Study RGB-14-101). The demographic and disease characteristics of the population at baseline was similar between the two treatment groups.

The primary efficacy endpoint was the percentage change in lumbar spine (LS) bone mineral density (BMD) assessed by DXA at week 52 compared to baseline. At the end of the Main period (i.e., Week 52), the difference in the mean percentage change from baseline in LS BMD between the RGB-14-P group and the US-Prolia group was 0.10 under the non-inferiority null imputation and 0.34 under the non-superiority null imputation of missing data, with the 90% confidence interval within the pre-defined equivalence margin of ±1.45% (Table 18). Therefore, this study demonstrated that there is no clinically meaningful difference between the two products with respect to efficacy. There was also no meaningful difference between RGB-14-P and US-Prolia with respect to the nature or frequency of treatment emergent adverse events.

The single transition from US-Prolia to RGB-14-P showed maintenance of efficacy (Table 20) and was not associated with any increase in the nature or frequency of adverse events or evidence of immunogenic response.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical analyses.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

Study RGB-14-101: A Randomized Double-blind, Multicenter Study to Assess the Efficacy and Safety of RGB-14-P Compared to US-Prolia in Women with Postmenopausal Osteoporosis

6.2.1. Data and Analysis Quality

There are no concerns regarding data quality and integrity.

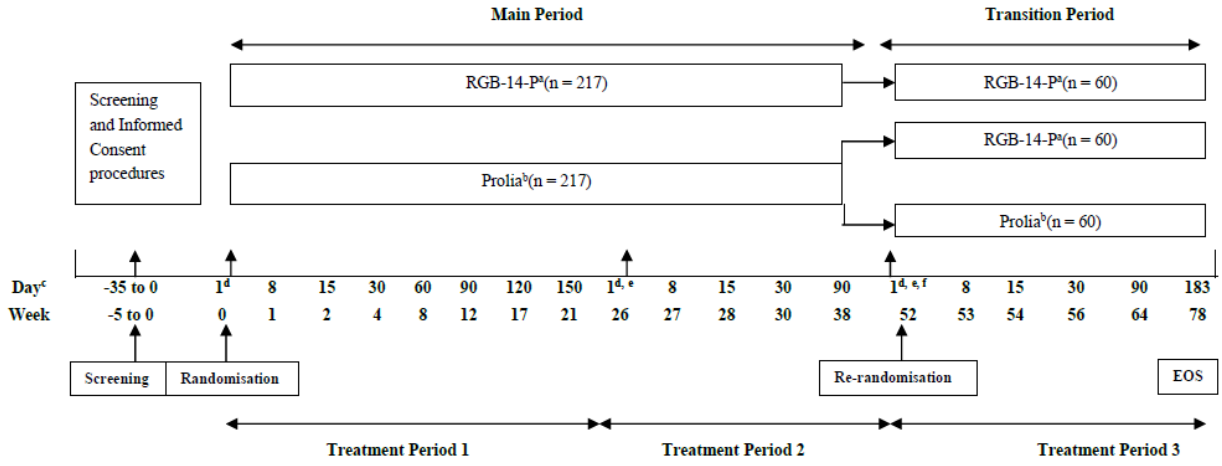
6.2.2. Study Design and Endpoints

Study RGB-14-101 was a randomized, double-blind, comparative clinical study consisting of two treatment periods. For the first treatment period (i.e., “Main Period”) a total of 473 female patients with post-menopausal osteoporosis (PMO) were

randomized in a 1:1 ratio to receive two doses of either 60 mg RGB-14-P (n = 242) or 60 mg US-Prolia (n = 231) subcutaneously (SC) on Day 1 and at Month 6.

At Month 12, the Transition Period commenced. Sixty-six patients in the RGB-14-P group continued treatment with a third dose of 60 mg SC RGB-14-P. Patients who had received US-Prolia in the Main Period were randomized in a 1:1 ratio to either continue on 60 mg SC US-Prolia (US-Prolia to US-Prolia, n = 63) or transitioned to 60 mg SC RGB-14-P (US-Prolia to RGB-14-P, n = 62). Patients were followed for an additional 6 months. The study design is shown in Figure 10.

Figure 10: Study RGB-14-101 design



EOS = End-of Study; n = number of participants

a. Test product
b. Reference product
c. Day(s) refer to days within Screening or Treatment Period
d. Dosing Visits
e. Day 1 of Treatment Periods 2 and 3 is also Day 183 of the preceding treatment period.
f. Participants continuing to the Transition Period who previously received Prolia® during the Main Period will be re-randomised 1:1 to either receive RGB-14-P or Prolia® in a double-blinded manner. Participants continuing to the Transition Period who received RGB-14-P during the Main Period will continue to receive a dose of RGB-14-P but will also follow the randomisation procedure to maintain blinding.

Source: Module 5.3.5.1, Clinical protocol RGB-14-101 Amendment 2, Version 5.0, Figure 1-2, page 15

To qualify for enrollment, patients had to be post-menopausal, aged 60 to 90 years (inclusive), and have osteoporosis according to bone mineral density (BMD) criteria on dual-energy Xray absorptiometry (DXA) scan (T-score ≥ -4.0 and ≤ -2.5 at the lumbar spine). Patients also had to be naïve to therapeutic monoclonal antibody or fusion receptor protein (including denosumab, denosumab biosimilar, or romosozumab). Refer to Section 14.3.2 for the list of key eligibility criteria.

RGB-14-P or US-Prolia were administered by authorized and blinded site staff into thigh, abdomen, or upper arm. The dose used in the trial is the same as the dose of US-Prolia indicated for treatment of post-menopausal osteoporosis (i.e., 60 mg SC every 6 months). All patients also received at least 1000 mg daily of elemental calcium and at least 800 IU daily of vitamin D or calcitriol, with adjustments made as necessary based on results of calcium and 25-hydroxy (OH) vitamin D levels during treatment.

The primary efficacy endpoint was the percent change in lumbar spine (LS) BMD assessed by DXA at Week 52 compared to baseline, performed in the Full Analysis Set (FAS; defined as all patients to whom the study drug has been randomized). The same DXA scanner was used for all study procedures for a particular patient at each site. All DXA scans were submitted to and analyzed centrally.

The secondary endpoints were intended to provide supportive evidence relating to the primary endpoint, and no formal adjustments for multiplicity were performed. Secondary efficacy endpoints included percent change from baseline in lumbar spine BMD to Week 26 and 78, analyzed similarly to the primary endpoint; and the percent change from baseline in total hip and femoral neck BMD at Week 26, 52, and 78.

The PD endpoint analyzed using an analysis of variance (ANOVA) model was the area under the effect time curve (AUEC) after first dose (AUEC0-M6) of percentage change from baseline in serum carboxy-terminal crosslinked telopeptides of type I collagen (CTX). Refer to Section 5.3.

The study entailed 20 visits to the study clinic, which included a screening visit, 14 visits during the Main Period, 4 visits during the Transition Period, and an End of Study visit at the end of the Transition Period. Assessments included periodic testing of vital signs, ECG prior to each study drug administration, and laboratory tests for safety. DXA scan was performed at screening and again at treatment Weeks 26, 52 and 78. Immunogenicity assessment consisted of anti-drug antibody (ADA) testing. The complete schedule of assessments is shown in Figure 11 and Figure 12, in the Appendices.

6.2.3. Statistical Methodologies

Analysis Population

The main period full analysis set (FAS) was defined as all patients who were randomized. The Applicant's primary efficacy analysis was performed using the full analysis set (FAS).

Primary Efficacy Analysis

The statistical hypotheses tested to assess similarity between RGB-14-P and US-Prolia in terms of the percent change from baseline in lumbar spine bone mineral density (LS-BMD) at week 52 (Tests 1 and 2 below, respectively) is as follows:

Test 1: for non-inferiority (delta = -1.45):

H_0: $\mu_{RGB\text{-}14\text{-}P} - \mu_{Prolia} \leq -1.45\%$

H_1: $-1.45\% < \mu_{RGB\text{-}14\text{-}P} - \mu_{Prolia}$

Test 2: for non-superiority (delta = 1.45):

H_0: $\mu_{RGB\text{-}14\text{-}P} - \mu_{Prolia} \geq +1.45\%$

H_1: $\mu_{RGB\text{-}14\text{-}P} - \mu_{Prolia} < +1.45\%$

where $\mu_{RGB-14-P}$ and μ_{Prolia} denotes the true mean % change from baseline in lumbar spine BMD at Week 52 for RGB-14-P and US-Prolia, respectively. A margin of ± 1.45% was used to determine clinical similarity.

Margin derivation for percent change from baseline in BMD for lumbar spine

The similarity margin, which was agreed upon by FDA, was based on three published clinical trials (Bone et al., 2008, Cummings et al., 2009 [pivotal FREEDOM trial], McClung et al., 2006). Based on this meta-analysis, the point estimate of the treatment effect of the reference product was 5.35% with 95% CI (4.83%, 5.87%). The Applicant stated that the lower bound of the 95% CI is used to justify an appropriate margin:

- A margin of 1.45% retains at least 70% of the treatment effect of the reference product.

The Applicant's prespecified primary analysis of the primary endpoint, the percent change from baseline in lumbar spine BMD at week 52, was performed using an analysis of covariance (ANCOVA) model. The model included treatment, stratification variables (previous use of bisphosphonates (yes/no) and geographical region (Europe, US)), baseline BMD value in lumbar spine, machine type (as per DXA scan external data transfer), and machine type * baseline BMD value interaction.

A penalty (delta of -1.45% and 1.45%) was applied to the imputed values for the RGB-14-P group reflecting the noninferiority and non-superiority null hypotheses (H_0), respectively, and two separate one-sided tests were performed at alpha=0.05. Comparative effectiveness between the two products is declared if both the lower and upper confidence limits for the difference in primary endpoint, based on the two one-sided tests, fall entirely within the pre-specified equivalence margins of +/-1.45%.

Missing data

There were 20 (8%) patients with missing data in the RGB-14-P arm and 23 (10%) in the US-Prolia arm at week 52. For the primary analysis using the ANCOVA model, if the week 52 BMD lumbar spine was missing for the US-Prolia arm, the corresponding value of the percent change from baseline was imputed assuming MAR and imputed assuming they would have behaved like patients in the same arm had they not have a missing value or taken prohibited medication. The RGB-14-P arm missing data was imputed using missing not at random (MNAR) method 'Under the Null': missing primary efficacy data were assumed to worsen from MAR by an amount of equivalence margin, ±1.45%. The Applicant also used the intermediate Week 26 data as a post-randomization predictive variable in both treatment arms. The imputation was run to produce 50 multiply imputed datasets.

FDA conducted an analysis on the primary endpoint using the FDA preferred analysis set with multiple imputation under the corresponding null for the two one-sided tests, testing for non-inferiority and non-superiority. To implement this imputation approach, FDA first imputed missing data of the RGB-14-P group using all observed data from the US-Prolia group and only baseline data from the RGB-14-P group. When imputing

missing values in the US-Prolia group, baseline data and intermediate endpoint values were included. After the multiple imputation, the imputed values of the RGB-14-P product group were further decreased by the similarity margin 1.45% when testing non-inferiority and added by the margin when testing non-superiority.

A two-dimensional tipping point analysis was conducted by the Applicant with a gradual shift in imputed values in each treatment group until the 90% CI was no longer entirely within the therapeutic similarity margin of ±1.45%.

Secondary endpoints

The secondary endpoints for the mean percentage change from baseline were as follows:

- Total hip BMD (TH-BMD) after 26 and 52 weeks
- Lumbar-spine BMD by DXA after 26 weeks
- Femoral neck BMD (FN- MD) at week 26 and 52 weeks.

These continuous endpoints were analyzed using a mixed model for repeated measures (MMRM). The model included treatment, stratification variables (previous use of bisphosphonates (yes/no) and geographical region (Europe, US)), baseline BMD value, machine type (as per DXA scan external data transfer), machine type * baseline BMD value interaction, study week, and study week*treatment interaction. No imputation for missing data was conducted on the secondary endpoints. There were no multiplicity adjustments made for the secondary endpoints.

6.2.4. Patient Disposition

The majority of patients in all treatment groups completed the Main Period and Transition Period (refer to Table 14 and Table 15, respectively). The most common reason for premature discontinuation in both treatment periods was patient withdrawal of consent.

Table 14: Patient disposition, Study RGB-14-101, Main Period

Status	RGB-14-P (N=242) n (%)	US-Prolia (N=231) n (%)
Randomized	242	231
Received at least 1 dose of the study drug	242 (100)	231 (100)
Completed Main Period	225 (93.0)	211 (91.3)
Discontinued treatment	17 (7.0)	20 (8.7)
Reason for treatment discontinuation [a]		
Withdrawal by patient	8 (3.3)	13 (5.6)
Adverse event	2 (0.8)	2 (0.9)
Lost to Follow-up	3 (1.2)	0
Death	0	1 (0.4)

Status	RGB-14-P (N=242) n (%)	US-Prolia (N=231) n (%)
Protocol deviation	1 (0.4)	0
Other [b]	2 (0.8)	2 (0.8)

Source: data compiled from Study RGB-14-101 ADSL dataset and the Module 5.3.5.1 Clinical Study Report for Study RGB-14-101, Table 10-1, pages 116-117.
[a] Reason for treatment discontinuation was not reported for patients (b) (6) and (b) (6) However, reasons for study discontinuation for these patients are listed as stop the study during the war in Ukraine (n=2) and study terminated by Sponsor (n=1).
[b] Other reasons for treatment discontinuation include an exclusion criterion has been found - more than three years of cumulative use of oral bisphosphonates prior the screening period (n=1); study objective confounded by monoclonal gammopathy (n=1); patient's personal reason (n=2).

Table 15: Patient disposition, Study RGB-14-101, Transition Period

Status	RGB-14-P to RGB-14-P (N=63) n (%)	US-Prolia to RGB-14-P (N=62) n (%)	US-Prolia to US-Prolia (N=63) n (%)
Re-randomized	63 (100)	62 (100)	63 (100)
Received 3rd dose of the study drug	63 (100)	62 (100)	63 (100)
Completed Transition Period	63 (100)	62 (100)	62 (98.4)
Discontinued treatment	0	0	1 (1.6)
Withdrawal by patient	0	0	1 (1.6)

Source: data compiled from Study RGB-14-101 ADSL dataset and the Module 5.3.5.1 Clinical Study Report for Study RGB-14-101, Table 10-1, pages 118

6.2.5. Demographics and Baseline Characteristics

Demographic characteristics were well-balanced between the two treatment groups, with the exception of a slight excess of patients with age less than 65 years in the RGB-14-P group (41.3%) compared to the US-Prolia group (37.2%) (Table 16). Baseline disease characteristics were also similar, with the exception of a slight imbalance of patients in the RGB-14-P group with a history of fracture (30.2%) and baseline serum vitamin D levels below the lower limit of normal (27.3%) compared to the US-Prolia group (26.0% and 35.1%, respectively) (Table 17). It is unlikely that these differences in baseline and demographic characteristics are significant or will impact the study findings.

Table 16: Demographic Characteristics, Study RGB-14-101

Demographic variable	RGB-14-P (N = 242)	US-Prolia (N = 231)
Mean (SD) age, years	66.7 (5.20)	66.8 (4.91)
Age, n (%)		
<65 years	100 (41.3)	86 (37.2)

Demographic variable	RGB-14-P (N = 242)	US-Prolia (N = 231)
≥65 years	142 (58.7)	145 (62.8)
Race, n (%)		
White	241 (99.6)	229 (99.1)
Black or African American	0	2 (0.9)
Native Hawaiian or other pacific islander	1 (0.4)	0
Mean (SD) weight, kg	64.0 (9.69)	65.1 (8.95)
Mean (SD) BMI kg/m^2	25.2 (3.48)	25.7 (3.76)
<25 kg/m^2	126 (52.1)	108 (46.8)
≥25 kg/m^2	116 (47.9)	123 (53.2)
Country, n (%)		
Poland	125 (51.7)	100 (43.3)
Bulgaria	40 (16.5)	27 (11.7)
Czech Republic	25 (10.3)	36 (15.6)
Hungary	19 (7.9)	20 (8.7)
Spain	13 (5.4)	22 (9.5)
Italy	8 (3.3)	15 (6.5)
United States	11 (4.5)	9 (3.9)
Ukraine	1 (0.4)	2 (0.9)

Source: Data compiled from Study RGB-14-101 ADSL dataset and the Module 5.3.5.1, Clinical Study Report for Study RGB-14-101, Table 10-5, pages 94-95.
Abbreviations: BMI = body mass index.

Table 17: Baseline Disease Characteristics, Study RGB-14-101

Characteristics	RGB-14-P (N = 242)	US-Prolia (N = 231)
Prior bisphosphonate use, n (%)		
Yes	17 (7.0)[a]	18 (7.8)
History of fracture (any), n (%)		
Yes	73 (30.2)	60 (26.0)
Baseline LS BMD (g/cm^2)		
Mean (SD)	0.8 (0.07)	0.8 (0.07)
Min, Max	0.617, 0.920	0.581, 0.897
Baseline LS T-score		
Mean (SD)	-3.1 (0.40)	-3.1 (0.43)
Min, Max	-4.1, -2.2	-4.1, -2.3
Serum 25-OH vitamin D <LLN		
n (%)	66 (27.3)	81 (35.1)

Source: data compiled from Study RGB-14-101 ADCM, ADMH, ADMK, ADLB2 dataset and the Module 5.3.5.1, Clinical Study Report for Study RGB-14-101, Table 14.1.6.1 in page 367, Table 14.2.1.1 in page 709.
Abbreviations: LS = lumbar spine; BMD = bone mineral density; LLN = lower limit of normal.

[a] This number differs by 1 compared to the Clinical Study Report for Study RGB-14-101, Table 14.1.6.1, because patient (b) (6) who had prior treatment of Fosavance was not counted in the Clinical Study Report table.

6.2.6. Analysis of Primary Clinical Endpoint(s)

Table 18 shows the results for the FDA's preferred analysis. In this analysis, the FDA imputed missing data under the corresponding null for two one-sided tests, one test for non-inferiority and the other test for non-superiority. Results from the two tests supported the conclusion of similarity.

Table 18. Primary Analysis of Percent Change in BMD for Lumbar Spine at Week 52, FAS Population

	RGB-14-P N=242	US-Prolia N=231
Baseline mean LS-BMD (SD)	0.77 (0.07)	0.78 (0.07)
Multiple imputation #1[1]		
LS Means	5.25	5.03
Treatment difference (RGB-14-P -Prolia)	0.10	
90% CI[2]	-0.52, 0.71	
Multiple imputation #2[1]		
LS Means	5.52	5.03
Treatment difference (RGB-14-P -Prolia)	0.34	
90% CI[2]	-0.27, 0.95	
Multiple imputation #3[1]		
LS Means	5.38	5.03
Treatment difference (RGB-14-P -Prolia)	0.22	
90% CI[2]	-0.29, 0.83	

Source: Statistical Reviewer's Analysis; adsl.xpt, admk.xpt
[1]Imputation #1: Subtract the imputed values by the margin, 1.45, to test non-inferiority
Imputation #2: Add the imputed values by the margin, 1.45, to test non-superiority.
Imputation #3: No penalty
[2] Primary objective met if the 90% CI for the difference between RGB-14-P and Prolia was contained within the pre-specified margin of (-1.45%, 1.45%).
Note: LS Means are from the analysis of covariance model with treatment (RGB-14-P, Prolia), stratification variables (previous use of bisphosphonates [yes/no] and geographical region [Europe, US])), baseline lumbar spine BMD machine type and machine type*baseline BMD value interaction.
Note: The treatment mean difference was calculated as RGB-14-P – Prolia.
Abbreviations: CI, confidence interval; LS, least squares; BMD, bone mineral density; N, total number of subjects; SD, standard deviation

Potential Effects of Missing Data

The applicant pre-specified a tipping point analysis for the primary endpoint using the FAS population. The results supported the primary analysis results. The similarity conclusion would be tipped under unlikely scenarios.

6.2.7. Analysis of Secondary Clinical Endpoint(s)

Although not controlled for type I error or subject to hypothesis testing, BMD values for femoral neck and total hip were assessed by DXA at Week 52, coinciding with the completion of twelve months of treatment prior to the single transition dose.

The difference between RGB-14-P and US-Prolia was estimated by the difference in the least squares means of percent change from baseline to Week 52, with 95% confidence intervals. At Week 52, the increase in percent change from baseline in femoral neck and total hip BMD was similar between the RGB-14-P and US-Prolia groups (Table 19). These data do not suggest a clinically meaningful difference between RGB-14-P and US-Prolia in efficacy at multiple skeletal locations.

Table 19: Analysis of percent change from baseline in femoral neck and total hip BMD (g/cm2) at Week 52, Full Analysis Set, Study RGB-14-101

	Treatment	LS means (95% CI)	Treatment difference (95% CI)
Total Hip BMD	RGB-14-P	2.16 (1.38, 2.94)	-0.16 (-0.68, 0.36)
	US-Prolia	2.32 (1.55, 3.10)	
Femoral Neck BMD	RGB-14-P	1.26 (0.18, 2.34)	-0.32 (-1.01, 0.36)
	US-Prolia	1.58 (0.51, 2.66)	

LS mean = least squares mean; SE = standard error; CI = confidence interval
Source: Clinical Study Report Table 11-7, page 139, and Table 11-17, page 154

There were no key efficacy confirmatory secondary endpoints prespecified in this study. There were no multiplicity adjustments made for the secondary endpoints. The results for the secondary endpoints considered exploratory are shown in the appendix.

Other Clinical Endpoint: Lumbar spine BMD at Week 78

Lumbar spine BMD values were assessed by DXA at Week 78, coinciding with six months after the single transition dose. The mean percent change from baseline in lumbar spine BMD at Week 78 was similar among the three treatment groups (Table 20). This endpoint was not controlled for type I error or subject to hypothesis testing. Nevertheless, these data do not suggest a clinically meaningful difference in efficacy after transitioning from US-Prolia to RGB-14-P.

Table 20: Analysis of percent change from baseline in lumbar spine BMD (g/cm2) at Week 72, Full Analysis Set, Study RGB-14-101

	RGB-14-P to RGB-14-P	US-Prolia to RGB-14-P	US-Prolia to US-Prolia
LS mean (95% CI)	7.03 (6.07, 8.00)	7.06 (5.96, 8.16)	7.09 (5.99, 8.19)

LS mean = least squares mean; CI = confidence interval
Source: Clinical Study Report Table 11-13, page 149

6.3. Review of Safety Data

6.3.1. Methods

Clinical Studies Used to Evaluate Safety

The evaluation of safety is based primarily on the comparative clinical study (Study RGB-14-101), which evaluated safety and efficacy of RGB-14-P and US-Prolia use in postmenopausal women with osteoporosis. However, safety data from the PK similarity study (Study RGB-14-001), which enrolled healthy adult males, was also examined for known risks of study drugs (e.g., hypersensitivity reactions and hypocalcemia) and to further evaluate any new safety signals that become apparent upon review of the comparative clinical study data. Safety analysis was conducted using the safety population, defined as patients who received at least one dose of the study drug. The size of the safety database was agreed upon with the Agency during the clinical development program.

Categorization of Adverse Events

In both study RGB-14-001 and study RGB-14-101, an adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of a study drug, whether or not considered related to the study drug. A treatment emergent adverse event (TEAE) was defined as an adverse event that starts or increases in severity on or after the first administration of the study treatment up to the end of the study or early termination visit following the last administration of study treatment. Abnormal laboratory values or other safety assessments constituted adverse events only if they were considered clinically significant.

Severity of all AEs was scored in a five-point scale as mild, moderate, severe, life threatening, or death. However, for injection site reactions that occurred in Study RGB-14-101, severity was scored based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.0.

Safety Analyses

Safety data were not combined because the study populations and design of the two studies differed.

Study RGB-14-101 consisted of two treatment periods. The first period compared the safety and efficacy of RGB-14-P to US-Prolia (Main Period) and the second period evaluated the safety of a transition from US-Prolia to RGB-14-P, compared to continuing on US-Prolia (Transition Period). Safety data from the two treatment periods are presented separately.

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

Study RGB-14-001 enrolled healthy adult male volunteers, who do not reflect the population for whom denosumab is indicated. Nonetheless, the population was considered appropriate and sensitive for the primary objectives of the study.

Study RGB-14-101 enrolled post-menopausal women with osteoporosis, which is one of the target populations for denosumab. Demographic and baseline disease characteristics of the study population are shown in Table 16 and Table 17, respectively.

Deaths

Study RGB-14-001

There were no deaths in this study.

Study RGB-14-101

One death occurred during the Main Period. A 64-year-old female with a history of cardiovascular disease, hypercholesterolemia, and hypertension randomized to US-Prolia experienced the fatal serious adverse event of myocardial infarction 53 days after the second dose of US-Prolia. An autopsy was not performed. The death was not considered related to the study drug, but rather to her underlying cardiac disease. Review of the narrative yields the same conclusion.

Serious Adverse Events

Study RGB-14-001

Two patients reported serious adverse events (SAE) during the study. One patient randomized to US-Xgeva experienced nerve compression on Day 170 and another patient randomized to RGB-14-X experienced influenza on Day 168. Upon review of the cases narratives, neither was considered to be related to study drug.

Study RGB-14-101

Main Period

During the Main Period, treatment-emergent SAEs occurred in 7/242 (2.9%) patients receiving RGB-14-P and 16/231 (6.9%) patients receiving US-Prolia. The excess SAE incidence in the US-Prolia group was driven by an excess number of cardiovascular disorders and malignancies.

SAE of fractures occurred in 1/242 (0.4%) patient receiving RGB-14-P and 1/231 (0.4%) patient receiving US-Prolia. The narratives for the two patients with SAEs of fracture are briefly summarized below:

- A 61-year-old white female with a history of ankle fracture and osteoporosis experienced radius fracture on Day 183 of the study, 1 day after the second dose of US-Prolia, following a fall on the sidewalk. At baseline, T-scores for lumbar spine, femoral neck, and femur were -2.7, -1.2, and -1.7. The patient was hospitalized and recovered after closed reposition and fixation with plaster. The patient continued the study through completion.
- A 65-year-old white female with a history of thoracic vertebral fracture and osteoporosis experienced humerus fracture on Day 189 of the study, 108 days after the second dose of RGB-14-P, following a fall at home due to imbalance. At baseline, T-scores for lumbar spine, femoral neck, and femur were -3.2, -3.1, and -2.6. The patient was hospitalized and recovered after undergoing an open reposition and fastening of the humerus fracture. The patient also underwent a neurological consultation due to reported frequent falls. The neurological examination concluded a possible Parkinsonism due to concomitant medication as a contributor to falls. The patient continued the study through completion.

Fractures AEs are further discussed below.

Other SAEs in the RGB-14-P group were chronic obstructive pulmonary disease and lumbosacral radiculopathy in one patient, anxiety disorder and panic attack in one patient, and osteoarthritis, meniscus injury, pneumonia, and thyroid cancer in one patient each. Refer to Table 21 for all SAEs reported during the Main Period of Study RGB-14-101.

Table 21: Serious adverse events, Study RGB-14-101, Main Period

Preferred Term	RGB-14-P (N=242)	US-Prolia (N=231)
Any SAE (%)	7 (2.9)	16 (6.9)
Acute coronary syndrome	0	1 (0.4)
Acute myocardial infarction	0	1 (0.4)
Anxiety disorder	1 (0.4)	0
Atrial fibrillation	0	1 (0.4)
Bladder cancer	0	1 (0.4)
Breast cancer	0	1 (0.4)

Preferred Term	RGB-14-P (N=242)	US-Prolia (N=231)
Cardiac disorder	0	1 (0.4)
Cardiac failure chronic	0	1 (0.4)
Chronic gastritis	0	1 (0.4)
Chronic obstructive pulmonary disease	1 (0.4)	1 (0.4)
Clear cell renal cell carcinoma	0	1 (0.4)
Coronary artery stenosis	0	1 (0.4)
Endometrial disorder	0	1 (0.4)
Humerus fracture	1 (0.4)	0
Invasive ductal breast carcinoma	0	1 (0.4)
Lumbosacral radiculopathy	1 (0.4)	0
Meniscus injury	1 (0.4)	1 (0.4)
Muscular weakness	0	1 (0.4)
Myocardial infarction	0	1 (0.4)
Osteoarthritis	1 (0.4)	0
Panic attack	1 (0.4)	0
Pneumonia	1 (0.4)	0
Primary gastrointestinal follicular lymphoma	0	1 (0.4)
Radius fracture	0	1 (0.4)
Renal neoplasm	0	1 (0.4)
Rotator cuff syndrome	0	1 (0.4)
Tendon rupture	0	1 (0.4)
Thyroid cancer	1 (0.4)	0

Source: clinical reviewer generated report

One SAE of clear cell renal carcinoma, which occurred in a 62-year-old female while receiving US-Prolia, was considered not related to the study drug by the Investigator but was considered related to US-Prolia by the Applicant, given the lack of alternative factors (e.g., absence of smoking history, personal or family history or other risk factors). This case is briefly reviewed below.

- A 62-year-old female with no relevant medical history was incidentally found to have a clear cell renal carcinoma on Day 266, 85 days after the second dose of US-Prolia, whilst undergoing a magnetic resonance imaging for other reasons. She was hospitalized, underwent successful left kidney neoformation enucleation, and was discharged on Day 273. No additional treatment was required. The event was classified as serious due to hospitalization. The patient completed the study but did not participate in the Transition Period.

None of the SAEs in either treatment group were considered related to study drug by the investigator. Review of the narratives yields the same conclusion. The single case of clear cell carcinoma that occurred in the US-Prolia group is likely due to chance and unlikely to represent a risk associated with US-Prolia treatment.

Transition Period

No SAEs occurred during the Transition Period.

Common Treatment Emergent Adverse Events

The review team conducted an analysis of AEs that occurred in study RGB-14-101 using OND Custom Medical Queries (OCMQ) and grouped queries (GQ). OCMQs are standardized groupings of similar adverse event terms intended to assist with the identification of potential safety issues during review of adverse event data. To further improve safety signal detection, the clinical review team also created GQs which consisted of adverse events that were not already part of an OCMQ but were synonymous. Patients who reported more than one individual preferred term grouped in a single OCMQ or GQ are only counted once in the number of patients reporting that combined term.

Study RGB-14-101

Main Period

Treatment emergent adverse events (TEAEs), listed by combined OCMQs or GQs, occurring at ≥3% frequency in either treatment group are listed in Table 22.

Overall, a similar proportion of patients in each treatment group reported at least one TEAE: 65.3% (158/242) in the RGB-14-P group and 65.8% (152/231) in the US-Prolia group. The most frequent TEAEs were comparable between treatment groups and aligned with denosumab's established safety profile or were typical for this patient population.

Table 22: Most common treatment emergent adverse events (i.e., reported by ≥3% of patients in either treatment group), Study RGB-14-101, Main Period

AE Term [a] Preferred term	RGB-14-P (N=242)	US-Prolia (N=231)	Risk Difference (%) (95% CI)
Any TEAE (%)	158 (65.3)	152 (65.8)	-
Nasopharyngitis	48 (19.8)	35 (15.2)	4.7 (-2.1, 11.5)
Nasopharyngitis	23 (9.5)	20 (8.7)	
Upper respiratory tract infection	23 (9.5)	10 (4.3)	
Pharyngitis	4 (1.7)	2 (0.9)	
Acute sinusitis	1 (0.4)	1 (0.4)	
Pharyngitis bacterial	1 (0.4)	0	
Rhinitis allergic	1 (0.4)	2 (0.9)	
Rhinitis	0	1 (0.4)	
Arthritis	14 (5.8)	4 (1.7)	4.1 (0.7, 7.4)
Osteoarthritis	10 (4.1)	3 (1.3)	
Spinal osteoarthritis	2 (0.8)	0	

AE Term [a] Preferred term	RGB-14-P (N=242)	US-Prolia (N=231)	Risk Difference (%) (95% CI)
Arthritis	1 (0.4)	1 (0.4)	
Synovitis	1 (0.4)	0	
Headache	14 (5.8)	4 (1.7)	4.1 (0.7, 7.4)
Headache	13 (5.4)	4 (1.7)	
Migraine	1 (0.4)	0	
Abdominal Pain	10 (4.1)	0	4.1 (1.6, 6.6)
Abdominal pain upper	7 (2.9)	0	
Abdominal pain	2 (0.8)	0	
Abdominal discomfort	1 (0.4)	0	
Lipid Disorder	13 (5.4)	4 (1.7)	3.6 (0.3, 6.9)
Hypercholesterolaemia	7 (2.9)	0	
Dyslipidaemia	3 (1.2)	0	
Hyperlipidaemia	2 (0.8)	1 (0.4)	
Type V hyperlipidaemia	1 (0.4)	0	
Blood cholesterol increased	0	3 (1.3)	
Dizziness	9 (3.7)	3 (1.3)	2.4 (-0.4, 5.2)
Dizziness	7 (2.9)	2 (0.9)	
Vertigo	2 (0.8)	1 (0.4)	
Dyspepsia	8 (3.3)	2 (0.9)	2.4 (-0.1, 5)
Abdominal pain upper	7 (2.9)	0	
Dyspepsia	2 (0.8)	2 (0.9)	
Diarrhea	8 (3.3)	4 (1.7)	1.6 (-1.2, 4.4)
Diarrhoea	8 (3.3)	4 (1.7)	
Arthralgia	12 (5.0)	10 (4.3)	0.6 (-3.2, 4.4)
Arthralgia	12 (5.0)	10 (4.3)	
Bacterial Infection	23 (9.5)	21 (9.1)	0.4 (-4.8, 5.6)
Urinary tract infection	11 (4.5)	11 (4.8)	
Helicobacter infection	2 (0.8)	2 (0.9)	
Cystitis	1 (0.4)	4 (1.7)	
Diverticulitis	1 (0.4)	1 (0.4)	
Erythema migrans	1 (0.4)	0	
Hordeolum	1 (0.4)	0	
Mastitis	1 (0.4)	0	
Mycobacterium tuberculosis complex test positive	1 (0.4)	0	
Paronychia	1 (0.4)	1 (0.4)	
Pharyngitis bacterial	1 (0.4)	0	
Pneumonia chlamydial	1 (0.4)	0	
Pulpitis dental	1 (0.4)	0	

AE Term [a] Preferred term	RGB-14-P (N=242)	US-Prolia (N=231)	Risk Difference (%) (95% CI)
Tooth abscess	1 (0.4)	0	
Urethritis	1 (0.4)	0	
Lyme disease	0	1 (0.4)	
Omphalitis	0	1 (0.4)	
Periodontitis	0	1 (0.4)	
Hypocalcemia	22 (9.1)	22 (9.5)	-0.4 (-5.7, 4.8)
Osteoporosis	5 (2.1)	7 (3.0)	-1 (-3.8, 1.9)
Lumbar vertebral fracture	2 (0.8)	1 (0.4)	
Spinal compression fracture	2 (0.8)	0	
Thoracic vertebral fracture	1 (0.4)	6 (2.6)	
Viral Infection	31 (12.8)	32 (13.9)	-1 (-7.2, 5.1)
COVID-19	24 (9.9)	24 (10.4)	
Influenza	3 (1.2)	4 (1.7)	
Herpes simplex	2 (0.8)	0	
Viral upper respiratory tract infection	2 (0.8)	2 (0.9)	
COVID-19 pneumonia	1 (0.4)	0	
Viral infection	1 (0.4)	0	
Bronchiolitis	0	1 (0.4)	
Bronchitis viral	0	1 (0.4)	
Herpes zoster	0	1 (0.4)	
Oral herpes	0	2 (0.9)	
Respiratory tract infection viral	0	1 (0.4)	
Renal and Urinary Tract Infection	13 (5.4)	15 (6.5)	-1.1 (-5.4, 3.1)
Urinary tract infection	11 (4.5)	11 (4.8)	
Cystitis	1 (0.4)	4 (1.7)	
Urethritis	1 (0.4)	0	
Bronchitis	2 (0.8)	8 (3.5)	-2.6 (-5.3,0)
Back Pain	11 (4.5)	17 (7.4)	-2.8 (-7.1, 1.5)
Spinal pain	7 (2.9)	4 (1.7)	
Back pain	2 (0.8)	8 (3.5)	
Lumbosacral radiculopathy	1 (0.4)	0	
Sacral pain	1 (0.4)	0	
Sciatica	1 (0.4)	6 (2.6)	
Fracture	9 (3.7)	18 (7.8)	-3.6 (-7.8, 0.5)
Foot fracture	2 (0.8)	1 (0.4)	
Lumbar vertebral fracture	2 (0.8)	1 (0.4)	
Spinal compression fracture	2 (0.8)	0	
Humerus fracture	1 (0.4)	1 (0.4)	

AE Term [a] Preferred term	RGB-14-P (N=242)	US-Prolia (N=231)	Risk Difference (%) (95% CI)
Thoracic vertebral fracture	1 (0.4)	6 (2.6)	
Tooth fracture	1 (0.4)	2 (0.9)	
Ankle fracture	0	1 (0.4)	
Forearm fracture	0	1 (0.4)	
Hand fracture	0	1 (0.4)	
Lower limb fracture	0	1 (0.4)	
Radius fracture	0	1 (0.4)	
Rib fracture	0	2 (0.9)	
Systemic Hypertension	8 (3.3)	16 (6.9)	-3.6 (-7.6, 0.4)
Hypertension	7 (2.9)	13 (5.6)	
Blood pressure increased	1 (0.4)	4 (1.7)	

Source: MAED analysis and clinical reviewer generated report
[a] Represents OCMQs, GQs and preferred terms (if not grouped in OCMQ or GQ). Grouping of several related terms in OCMQs/GQs rendered incidence that is different from the Applicant's analysis.

The TEAEs reported more frequently in RGB-14-P group by at least 1% compared to US-Prolia group were nasopharyngitis, arthritis, headache, abdominal pain, lipid disorder, dizziness, dyspepsia, and diarrhea. All of these TEAEs except one were mild or moderate in severity. One severe and serious case of arthritis was reported in RGB-14-P group, however, review of the narrative showed that it is unlikely to be related to RGB-14-P. Many of these TEAEs align with adverse events listed in the US-Prolia label. Comparable adverse events and their incidences in patients with osteoporosis treated with Prolia include upper respiratory tract infection (4.9%), pharyngitis (2.3%), musculoskeletal pain (7.6%), bone pain (3.7%), abdominal pain upper (3.3%), and vertigo (5.0%). TEAEs not specifically listed in the label (such as headache, lipid disorder, and diarrhea) are commonly observed in this patient population.

Notably, 10 cases of abdominal pain (grouped preferred term: abdominal pain upper, abdominal pain, and abdominal discomfort) were reported exclusively in RGB-14-P group. All were mild (n = 6) or moderate (n = 4) in severity, with none classified as severe or serious. Excluding one case with an unknown start date, the time to onset ranged from Day 1 to Day 167. Eight patients experienced a single event each, while the remaining 2 patients had recurrent events (2 events each). All recurrent events occurred after the first dose but before the second dose of RGB-14-P. All events, except for one case of abdominal pain, were reported as recovered or resolved. All events were considered unrelated to the study drug by the investigator and did not lead to study discontinuation.

For all common TEAEs discussed above, the differences between incidences were small and likely due to chance, rather than to meaningful differences between the products. The vast majority of cases in patients treated with RGB-14-P were not serious or severe, nor did they require changes to RGB-14-P dosing or other significant interventions. Therefore, these differences do not represent a clinically meaningful

safety difference between the two products and are not considered an unacceptable risk.

Transition Period

TEAEs, listed by combined OCMQs or GQs, occurring at ≥3% frequency in any of the treatment groups are listed in Table 23.

Overall, comparable proportion of patients in each group reported at least one TEAE. The most common TEAEs were similar across treatment groups and were consistent with the known safety profile of denosumab or were typical in this patient population.

Table 23: Most common treatment emergent adverse events (i.e., reported by ≥3% of patients in any treatment groups), Study RGB-14-101, Transition Period

AE Term[a] Preferred term	**RGB-14-P to RGB-14-P (N=63)**	**US-Prolia to RGB-14-P (N=62)**	**US-Prolia to US-Prolia (N=63)**	**Risk Difference US-Prolia to RGB-14-P vs. US-Prolia to US-Prolia % (95% CI)**	**Risk Difference US-Prolia to RGB-14-P vs. RGB-14-P to RGB-14-P % (95% CI)**
Any TEAE (%)	30 (47.6)	25 (40.3)	25 (39.7)	-	-
Lipase increased	0	3 (4.8)	1 (1.6)	3.3 (-2.9, 9.4)	4.8 (-0.5, 10.9)
Local Administration Reaction	0	3 (4.8)	1 (1.6)	3.3 (-2.9, 9.4)	4.8 (-0.5, 10.2)
Injection site erythema	0	1 (1.6)	0		
Injection site haematoma	0	0	1 (1.6)		
Injection site urticaria	0	2 (3.2)	0		
Viral Infection	4 (6.3)	2 (3.2)	0	3.2 (-1.2, 7.6)	-3.1 (-10.6, 4.3)
COVID-19	3 (4.8)	2 (3.2)	0		
Herpes simplex	1 (1.6)	0	0		
Urticaria	0	2 (3.2)	0	3.2 (-1.2, 7.6)	3.2 (-1.2, 7.6)
Injection site urticaria	0	2 (3.2)	0		
Back Pain	5 (7.9)	1 (1.6)	0	1.6 (-1.5, 4.7)	-6.3 (-13.7, 1.1)
Back pain	4 (6.3)	1 (1.6)	0		
Spinal pain	1 (1.6)	0	0		
Fracture	4 (6.3)	3 (4.8)	1 (1.6)	1.6 (-3.7, 7)	-3.1 (-10.6, 4.3)
Thoracic vertebral fracture	2 (3.2)	0	1 (1.6)		
Forearm fracture	1 (1.6)	0	0		
Lumbar vertebral fracture	1 (1.6)	2 (3.2)	0		

AE Term[a] Preferred term	RGB-14-P to RGB-14-P (N=63)	US-Prolia to RGB-14-P (N=62)	US-Prolia to US-Prolia (N=63)	Risk Difference US-Prolia to RGB-14-P vs. US-Prolia to US-Prolia % (95% CI)	Risk Difference US-Prolia to RGB-14-P vs. RGB-14-P to RGB-14-P % (95% CI)
Foot fracture	0	0	1 (1.6)		
Osteoporosis	3 (4.8)	2 (3.2)	1 (1.6)	1.6 (-3.7, 7)	-1.5 (-8.4, 5.3)
Thoracic vertebral fracture	2 (3.2)	0	1 (1.6)		
Lumbar vertebral fracture	1 (1.6)	2 (3.2)	0		
Arthralgia	0	2 (3.2)	1 (1.6)	1.6 (-3.7, 7)	3.2 (-1.2, 7.6)
Arthralgia	0	2 (3.2)	1 (1.6)		
Bacterial Infection	5 (7.9)	2 (3.2)	2 (3.2)	0.1 (-6.1, 6.2)	-4.7 (-12.7, 3.3)
Urinary tract infection	2 (3.2)	0	2 (3.2)		
Cystitis	1 (1.6)	0	0		
Periodontitis	1 (1.6)	0	0		
Pharyngitis bacterial	1 (1.6)	0	0		
Diverticulitis	0	1 (1.6)	0		
Furuncle	0	1 (1.6)	0		
Systemic Hypertension	2 (3.2)	1 (1.6)	1 (1.6)	0 (-4.4, 4.4)	-1.6 (-6.9, 3.8)
Blood pressure increased	1 (1.6)	0	0		
Hypertension	1 (1.6)	1 (1.6)	1 (1.6)		
Hypocalcemia	3 (4.8)	1 (1.6)	2 (3.2)	-1.6 (-6.9, 3.8)	-3.1 (-9.3, 3)
Hypocalcaemia	3 (4.8)	1 (1.6)	2 (3.2)		
Depression	0	0	2 (3.2)	-3.2 (-7.5, 1.2)	0
Depression	0	0	2 (3.2)		
Renal and Urinary Tract Infection	3 (4.8)	0	2 (3.2)	-3.2 (-7.5, 1.2)	-4.8 (-10, 0.5)
Urinary tract infection	2 (3.2)	0	2 (3.2)		
Cystitis	1 (1.6)	0	0		
Nasopharyngitis	6 (9.5)	3 (4.8)	6 (9.5)	-4.7 (-13.7, 4.3)	-4.7 (-13.7, 4.3)
Acute sinusitis	2 (3.2)	0	0		
Nasopharyngitis	1 (1.6)	2 (3.2)	4 (6.3)		
Pharyngitis bacterial	1 (1.6)	0	0		

AE Term[a] Preferred term	RGB-14-P to RGB-14-P (N=63)	US-Prolia to RGB-14-P (N=62)	US-Prolia to US-Prolia (N=63)	Risk Difference US-Prolia to RGB-14-P vs. US-Prolia to US-Prolia % (95% CI)	Risk Difference US-Prolia to RGB-14-P vs. RGB-14-P to RGB-14-P % (95% CI)
Rhinitis allergic	1 (1.6)	0	0		
Upper respiratory tract infection	1 (1.6)	1 (1.6)	2 (3.2)		

Source: MAED analysis and clinical reviewer generated report
[a] Represent terms that are combined OCMQs, GQs or preferred terms (if not grouped in OCMQ or GQ). Grouping of several related terms in OCMQs/GQs rendered incidence that is different from the Applicant's analysis.

The common TEAEs reported more frequently in Prolia to RGB-14-P transition group by at least 1% compared to other two groups were lipase increased, local administration reaction, viral infection, urticaria, back pain, fracture, osteoporosis, and arthralgia. All of these TEAEs were mild or moderate in severity and none were serious.

Lipase increased were observed in 3 (4.8%) patients (1 event each) in the US-Prolia to RGB-14-P group compared to 1 (1.6%) patient (1 event) in the US-Prolia to US-Prolia group, and none in the RGB-14-P to RGB-14-P group. The 3 cases in the US-Prolia to RGB-14-P group occurred between 1 and 90 days after the third dose of the study drug (i.e., the dose given during the transition period). All 3 cases were considered unrelated to the study drug by the investigator and were reported as recovered or resolved. None of the 3 patients reported an AE of pancreatitis. Actions taken as a response to these events were reported as re-testing (n=1) or none (n=2). Notably, the incidence of patients whose lipase levels shifted from baseline normal levels to higher than normal range were similar between the groups.

Back pain and arthralgia are similar to adverse events listed on the US-Prolia label (specifically, musculoskeletal pain with a 7.6% incidence rate for US-Prolia). Viral infection is a commonly anticipated event in this patient population. The OCMQ for osteoporosis captured patients who reported fracture events (preferred terms captured by OCMQ include: lumbar vertebral fracture and thoracic vertebral fracture). Hypocalcemia, fractures, local administration reactions (including urticaria) are further discussed in Section 6.3.3.

The slight imbalances in these common TEAEs between groups are unlikely to represent a clinically meaningful safety difference between the transition groups and are not considered an unacceptable risk.

Discontinuations due to Adverse Events

Study RGB-14-101

Main Period

A marginally higher proportion of patients in the US-Prolia arm (3/231 [1.3%]) discontinued treatment prematurely due to a TEAE compared to the RGB-14-P arm (2/242 [0.8%]).

Refer to Table 24 for all TEAEs leading to treatment discontinuation in the Main Period of Study RGB-14-101.

Table 24: Treatment emergent adverse events leading to treatment discontinuation, Study RGB-14-101, Main Period

	RGB-14-P (N=242)	US-Prolia (N=231)
Any AE (%)	2 (0.8)	3 (1.3)
Breast cancer	0	1 (0.4)
Myocardial infarction	0	1 (0.4)
Osteitis	1 (0.4)	0
Primary gastrointestinal follicular lymphoma	0	1 (0.4)
Thyroid cancer	1 (0.4)	0

Source: clinical reviewer generated report

Transition Period

No TEAEs leading to discontinuation of study drug were reported during this period given that all patients received one dose of the study drug.

Overall, treatment discontinuations were rare and the events leading to discontinuation do not appear to represent a clinically significant signal.

6.3.3. Additional Safety Evaluations

Laboratory Findings

Laboratory testing schedule and overall finding

Study RGB-14-001

Safety laboratory testing including hematology and serum chemistry (including serum calcium, ionized calcium, and phosphorus) occurred at screening, 1 day prior to the study drug administration, 8 hours post-dose, and days 2, 8, 14, then weeks 4, 13, 21 and 36 (end of study visit). Serum 25-hydroxyvitamin D level was assessed at screening only. Urinalysis was collected on the same days as hematology and chemistry, except it

was not collected at 8 hours post-dose. There were no meaningful differences between treatment groups in median change in these parameters over time.

Study RGB-14-101

Main Period

The safety laboratory testing including hematology and serum chemistry (including serum calcium, phosphorus, magnesium) occurred at screening, on Day 1 (prior to first study drug administration), Week 1, 2, 4, 12, and Week 26 (prior to second study drug administration), 27, 28, 30 , 38, and 52 (at the end of the Main Period). Serum 25-hydroxyvitamin D levels were assessed at screening and the day of study drug administration. Urinalysis was collected at screening, the day of study drug administration, and at Week 52. There were no meaningful differences between treatment groups in median change in these parameters over time during Main Period.

Transition Period

During the Transition Period, safety laboratory testing same as in the Main Period occurred on Week 52 (i.e., the day of study drug administration, labs collected pre-dose), and Week 53, 54, 56, 65 (i.e., 1, 2, 4, and 12 weeks following the third and final injection), as well as Week 78 (at the end of the Transition Period). Serum 25-hydroxyvitamin D levels were assessed on the day of the third injection only. Urinalysis was collected at screening and at Week 78. There were no meaningful differences between treatment groups in median change in these parameters over time during the Main Period.

Calcium and mineral levels

Denosumab can cause hypocalcemia and disturbances in bone-related mineral levels (i.e., reduced phosphorous and magnesium). The US-Prolia package insert advises that calcium, phosphorous and magnesium levels are monitored within 14 days of injection, especially for those at risk of disturbances of mineral metabolism. Therefore, this review includes a shift analysis of these laboratory parameters.

The Applicant did not provide specific severity grading for laboratory abnormalities other than information on whether the abnormalities were considered clinically significant. For the purpose of this review, hypocalcemia and hypomagnesemia are graded for severity using the laboratory cutoffs found in Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Table 25). Because CTCAE grading for hypophosphatemia is based on clinical symptoms and requirement for intervention rather than on specific levels, laboratory values for serum phosphorus are not graded using this method.

Table 25: CTCAE Toxicity Grading for Hypocalcemia and Hypomagnesemia

	Toxicity grade				
	1	2	3	4	5
Hypocalcemia					
Serum calcium (mg/dL)	<LLN – 8	<8-7	<7-6	<6	Death
Ionized calcium (mmol/L)	<LLN-1.0	<1.0-0.9	<0.9-0.8	<0.8	Death

	Toxicity grade				
	1	2	3	4	5
Hypomagnesemia (mg/dL)	<LLN-1.2	1.2-0.9	0.9-0.7	<0.7	Death

Source: US Department of Health and Human Services. (Nov. 27, 2017). Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The Applicant provided results for serum calcium and ionized calcium for subjects in Study RGB-14-001 and serum calcium and albumin-corrected serum calcium for patients in Study RGB-14-101. Because approximately 40% of total body calcium is protein bound, serum calcium may be artificially low in the setting of hypoalbuminemia and artificially high in the setting of hyperalbuminemia. In those situations, ionized calcium is preferred over albumin-corrected serum calcium levels given the reported inaccuracies with various correction formulas.[3]

Majority (152 of 165 [92.1%]) of the subjects in Study RGB-14-001 had normal albumin levels at baseline. The remaining 13 of 165 (7.9%) had high baseline albumin levels, with similar proportions between groups (8 of 83 [9.6%] from RGB-14-X group and 5 of 82 [6.1%] from US-Xgeva group). No subjects developed hypoalbuminemia during the study, however, 38 (23.0%) of all subjects developed hyperalbuminemia at some point during the study. Hence, for Study RGB-14-001, serum calcium measurements were examined for all subjects with normal albumin and ionized calcium levels were examined for subjects with hyperalbuminemia to account for potential artificial inflation of serum calcium measurements.

All patients in Study RGB-14-101 had normal albumin levels at baseline. During the Main Period, no patients developed hypoalbuminemia, while 2 patients developed hyperalbuminemia. These two patients' albumin levels marginally exceeded the upper limit of normal by 0.1 g/dL, likely not significantly affecting reported serum calcium accuracy. Hence, for this study, only total serum calcium levels were examined.

Notably, hypocalcemia risk increases with severe renal impairment or inadequate calcium/vitamin D intake. All patients from both studies were required to have a normal serum calcium level at enrollment. Study RGB-14-001 excluded subjects with significant creatinine levels, while RGB-14-101 excluded those with estimated glomerular filtration rate <30 mL/min or on dialysis. Following US-Prolia label recommendations, all patients in both studies were required to take ≥1000mg calcium and ≥800 IU vitamin D or calcitriol daily from first dose until end of the study or early termination.

Hypocalcemia

Study RGB-14-001

There were no reported adverse events of hypocalcemia. The incidence of hypocalcemia per laboratory assessments (i.e., serum calcium below the lower limit of normal) during the study was similar between the treatment groups (16/83 [19.3%] in RGB-14-X group versus 13/82 [15.9%] in US-Xgeva group). The median change from

[3] Lian IA, Åsberg A. Should total calcium be adjusted for albumin? A retrospective observational study of laboratory data from central Norway. BMJ Open. 2018 Apr 7;8(4):e017703

baseline in serum calcium was also comparable throughout. No patient from either group had serum calcium level below 8 mg/dL at any point during the study.

The incidence of hypocalcemia by ionized calcium levels for patients who developed hyperalbuminemia during the study was also similar between the treatment groups (10/27 [37.0%] in RGB-14-X group versus 12/24 [50%] in US-Xgeva group). The median change from baseline in ionized calcium was also comparable. No patient from either group had ionized calcium level below 1.0 mmol/L at any point during the study.

Among the patients with laboratory evidence of hypocalcemia, none were considered clinically significant.

Study RGB-14-101

Main Period

The median change from baseline in serum calcium was comparable in both treatment groups throughout the Main Period (Table 26).

Table 26: Median (Min, Max) change from baseline in serum calcium (mg/dL) following the study drug administration, Main Period, Study RGB-14-101

	RGB-14-P (N=242)	US-Prolia (N=231)
Week 1	-0.3 (-1.72, 0.84) n=238	-0.3 (-2.16, 1.2) n=227
Week 2	-0.2 (-1.6, 2.72) n=236	-0.2 (-1.84, 1.2) n=225
Week 4	-0.2 (-1.3, 0.96) n=238	-0.2 (-2.36, 1.4) n=225
Week 12	-0.3 (-1.28, 1.56) n=233	-0.2 (-2, 1.24) n=223
Week 26*	-0.1 (-1.04, 1.28) n=227	-0.1 (-1.12, 1.6) n=218
Week 27	-0.2 (-1.24, 1.08) n=209	-0.1 (-1.92, 1.48) n=205
Week 28	-0.1 (-1.2, 1.16) n=201	-0.1 (-1.2, 1.48) n=192
Week 30	-0.1 (-1.16, 1.12) n=223	-0.1 (-1.2, 1.8) n=216
Week 38	-0.1 (-1.2, 1.08) n=224	-0.1 (-1.2, 1.96) n=215
Week 52	0.0 (-1.12, 1.36) n=225	0.0 (-1.4, 1.3) n=208

n=number of patients with lab values
*Second study drug administration occurred on Week 26 and the labs were collected pre-dose.
Source: Clinical reviewer analysis

The incidence of reported hypocalcemia adverse events was similar between the two treatment groups and occurred in 22 (9.1%) subjects in the RGB-14-P group and 22

(9.5%) subjects in the US-Prolia group. All were mild in severity except for events that occurred in 3 subjects in the RGB-14-P group, which were moderate in severity. None were serious nor considered related to the study drug.

The incidence of hypocalcemia by laboratory assessment (i.e., serum calcium below the lower limit of normal) during the Main Period was also similar between the two treatment groups. Most of the shifts occurred following the first dose of the study drug (Table 27).

Table 27: Number (%) of patients with shift in serum calcium to below the lower limit of normal after first or second study drug administration during the Main Period, Study RGB-14-101

	RGB-14-P (N=242)	US-Prolia (N=231)
Number of patients with normal or elevated calcium at baseline	242 (100.0)	231 (100.0)
Hypocalcemia at any time during the Main Period	17 (7.0)	24 (10.4)
Following first study drug injection		
During the first 2 weeks post-injection #1	4 (1.7)	13 (5.6)
Between 4 weeks and 26 weeks post-injection	10 (4.1)	10 (4.3)
Following second study drug injection		
During the first 2 weeks post-injection #2	4 (1.7)	4 (1.7)
Between 4 weeks and 26 weeks post-injection	1 (0.4)	7 (3.0)

Source: Clinical reviewer analysis

Among the patients with laboratory evidence of hypocalcemia, none were considered clinically significant or symptomatic, with mild and comparable declines between groups. No Grade ≥2 hypocalcemia (i.e., calcium values below 8 mg/dL) occurred in the RGB-14-P group. In the US-Prolia group, one patient experienced Grade 2 hypocalcemia 8 days after the second dose but recovered to normal levels by the end of Main Period.

The serum calcium levels of all patients in the RGB-14-P group whose levels shifted to below the lower limit of normal returned to normal levels by the end of the Main Period. All but three patients in the US-Prolia group whose levels shifted to below the lower limit of normal had returned to normal levels by the end of the Main Period.

Transition Period

Patients who continued to Transition Period received their third and final dose of the study drug at Week 52.

The median change from baseline in serum calcium was comparable in all three groups (Table 28).

Table 28: Median (Min, Max) change from baseline in serum calcium following third study drug administration, Transition Period, Study RGB-14-101

	RGB-14-P to RGB-14-P (N=63)	US-Prolia to RGB-14-P (N=62)	US-Prolia to US-Prolia (N=63)
Week 53	0.0 (-1.08, 0.96) n=61	0.0 (-1.2, 1) n=59	0.0 (-0.96, 1.12) n=62
Week 54	-0.1 (-0.88, 1.2) n= 62	-0.1 (-1.28, 1.2) n=61	0.0 (-0.80, 1.4) n=62
Week 56	0.0 (-0.92, 1.48) n=57	0.0 (-0.80, 0.9) n=53	-0.1 (-0.92, 1.28) n=57
Week 64	0.0 (-0.80, 1.28) n=63	0.1 (-1.44, 1.1) n=62	0.0 (-0.76, 0.76) n=62
Week 78	.1 (-1.08, 0.72) n=63	0.0 (-1.52, 1.2) n=62	-0.1 (-0.88, 0.92) n=61

n=number of patients with lab values
Source: Clinical reviewer analysis

The adverse event of hypocalcemia occurred in 3 (4.8%) subjects in the RGB-14-P to RGB-14-P group, 1 (1.6%) subject in the US-Prolia to RGB-14-P group, and 2 (3.2%) subjects in the US-Prolia to US-Prolia group. One event each from the US-Prolia to RGB-14-P group and the US-Prolia to US-Prolia group was moderate in severity and the rest were mild in severity. All were non-serious and not considered related to the study drug.

Based on the laboratory assessment, a slightly higher proportion of patients in the RGB-14-P to RGB-14-P group developed hypocalcemia compared to the other two groups (Table 29). Among the patients with laboratory evidence of hypocalcemia, none were considered clinically significant or symptomatic. No patient had serum calcium level <8 mg/dL.

Based on the above, the small differences in the incidence of hypocalcemia per reported event or laboratory assessment by different treatment groups in both the Main Period and the Transition Period are unlikely to be meaningful and likely due to chance.

Table 29: N (%) of patients with a shift in serum calcium from normal or elevated at Transition Period baseline (i.e., Week 52) to below the lower limit of normal (<LLN) during Study RGB-14-101, Transition Period

	RGB-14-P to RGB-14-P (N=63)	US-Prolia to RGB-14-P (N=62)	US-Prolia to US-Prolia (N=63)
Number of patients with normal or elevated serum calcium at Week 52	63 (100.0)	62 (100.0)	62 (98.4)
Calcium shift to <LLN	3 (4.8)	1 (1.6)	1 (1.6)

Calcium shift to <8 mg/dL	0	0	0

LLN=lower limit of normal
Source: Clinical reviewer analysis

Hypophosphatemia and hypomagnesemia

Study RGB-14-001

There were no reported adverse events of hypomagnesemia events. The proportion of patients shifting from normal/high baseline to below-normal serum phosphorus was common but similar between groups (43/83 [51.8%] in RGB-14-X group vs 34/82 [41.5%] in US-Xgeva group). Most recovered to normal range by the end of study (33/43 [76.7%] in RGB-14-X group, 31/34 [91.2%] in US-Xgeva group). No shifts were considered clinically significant. The minor difference in phosphorus level shifts between groups are likely due to chance and other factors (e.g., dietary phosphorus intake) rather than study drug differences.

This study did not assess serum magnesium levels.

Study RGB-14-101

There were no reported adverse events related to hypophosphatemia in any treatment groups for both the Main Period and the Transition Period. The overall incidence of adverse events related to hypomagnesemia was low and similar between the treatment groups. During the Main Period, the event was reported in 1 (0.4%) subject in the RGB-14-P group (with the preferred term: magnesium deficiency) and 2 (0.9%) subjects in the US-Prolia group (with the preferred terms: blood magnesium decreased and hypomagnesaemia). During the Transition Period, one event of blood magnesium decreased was reported in the RGB-14-P to RGB-14-P group. All reported events related to hypomagnesemia were mild in severity, non-serious, and assessed as not related to the study drug.

Laboratory assessments showed that the proportion of patients shifting from normal/high baseline to below-normal for serum phosphorus and magnesium were similar between treatment groups for both Main Period (Table 30) and Transition Period (Table 31). In both periods, no shifts were considered clinically significant, and no Grade ≥2 hypomagnesemia cases occurred.

All patients with laboratory evidence of hypophosphatemia during the Main Period recovered to normal, except for 2 patients in RGB-14-P group who developed it on the last day of the Main Period (Day 183). Most hypomagnesemia cases normalized, with similar rates of persistent cases between the groups at the end of the Main Period (4 [1.8%] patients from RGB-14-P group and 3 [1.4%] patients from US-Prolia group). None of these were reported as an adverse event.

In the Transition Period, all who developed hypomagnesemia recovered to normal levels by the end except for 2 patients in the RGB-14-P to RGB-14-P group and 2 patients in the US-Prolia to US-Prolia group. None of these were reported as an adverse event.

The minor differences in the incidence of adverse events and shifts of these laboratory parameters between the treatment groups for both periods likely stem from chance rather than differences in the study drugs.

Table 30: Number (%) of patients with shifts in phosphorus or magnesium to below the lower limit of normal during Main Period, Study RGB-14-101

Laboratory parameter	RGB-14-P N= 242	US-Prolia N= 231
Phosphorus	5 (2.1) n=242	2 (0.9) n=231
Magnesium	9 (3.8) n=236	15 (9.7) n=225

n = number of patients with normal or elevated values at baseline
Source: Clinical reviewer analysis

Table 31: Number (%) of patients with shifts in phosphorus or magnesium to below the lower limit of normal during Transition Period, Study RGB-14-101

Laboratory parameter	RGB-14-P to RGB-14-P (N=63)	US-Prolia to RGB-14-P (N=62)	US-Prolia to US-Prolia (N=63)
Phosphorus	0 n=63	0 n=62	0 n=62
Magnesium	3 (4.8) n=63	2 (3.2) n=62	5 (7.9) n=62

n = number of patients with normal or elevated values at baseline
Source: Clinical reviewer analysis

Hemoglobin levels

Denosumab was associated with a higher incidence of anemia in the US-Prolia post-menopausal osteoporosis indication registration trial. Therefore, this review includes ananalysis of changes in hemoglobin levels.

The CTCAE toxicity grading scale for anemia is shown in Table 32 with toxicity levels based on laboratory values.

Table 32: CTCAE Toxicity Grading Scale for Anemia

	Toxicity Grade				
	1	**2**	**3**	**4**	**5**
Anemia	<LLN – 10 g/dL	<10 – 8 g/dL	<8 g/dL, Transfusion indicated	Life-threatening consequences, urgent intervention needed	Death

Source: US Department of Health and Human Services. (Nov. 27, 2017). Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Study RGB-14-001

In this study, no patient reported an adverse event related to anemia. US-Xgeva group showed higher rates of hemoglobin shifts from normal/high baseline to below-normal (7/83 [8.4%] in RGB-14-X group versus 15/82 [18.3%] in US-Xgeva group). All but one patient from RGB-14-X group and 2 patients from US-Xgeva group normalized by the end of the study. No patients had hemoglobin below 10 g/dL (Grade ≥2) or clinically significant shifts.

Study RGB-14-101

Main Period

The incidence of adverse event of anemia was low and similar between the treatment groups (with 2 [0.8%] patients from the RGB-14-P group reporting mild events and 1 [0.4%] patient from the US-Prolia group reporting a moderately severe event). None were serious nor considered related to the study drug.

The laboratory assessment showed that RGB-14-P group had slightly higher rates of hemoglobin shifts from normal/high baseline to below-normal compared to US-Prolia. The proportion of patients who had low hemoglobin levels at the end of the Main Period was also slightly higher in RGB-14-P group (6 [2.7%] patients from RGB-14-P group versus 2 [1.0%] patients from US-Prolia group). No patient had hemoglobin below 10 g/dL (Table 33) and none of these patients reported adverse events related to anemia. This transient, mild hemoglobin shift difference is unlikely clinically meaningful.

Table 33: Number (%) of patients with shift in hemoglobin to below the lower limit of normal or below 10 g/dL during the Main Period, Study RGB-14-101

Laboratory parameter	RGB-14-P N= 242	US-Prolia N= 231
Hemoglobin shift to <LLN	21 (9.3) n=227	12 (5.4) n=221
Hemoglobin shift to <10 g/dL	0	0

n = normal or elevated values at baseline; LLN = lower limit of normal
Source: Clinical reviewer analysis

Transition Period

There were no adverse event of anemia reported during the Transition period in any of the treatment groups. Laboratory assessment showed that hemoglobin shifts from normal/high baseline to below-normal were also comparable between the groups. No patient's hemoglobin dropped below 10 g/dL (Table 34).

Table 34: Number (%) of patients with shift in hemoglobin to below the lower limit of normal or below 10 g/dL during the Main Period, Study RGB-14-101

Laboratory parameter	**RGB-14-P to RGB-14-P (N=63)**	**US-Prolia to RGB-14-P (N=62)**	**US-Prolia to US-Prolia (N=63)**
Hemoglobin shift to <LLN	4 (6.3)	5 (8.1)	3 (4.8)

Laboratory parameter	RGB-14-P to RGB-14-P (N=63)	US-Prolia to RGB-14-P (N=62)	US-Prolia to US-Prolia (N=63)
Hemoglobin shift to <10 g/dL	0	0	0

n = normal or elevated values at baseline; LLN = lower limit of normal
Source: Clinical reviewer analysis

Other Laboratory Findings

In Study RGB-14-001, one male patient of 49 years of age experienced clinically significant liver enzyme shifts on Day 147, reported as a non-serious, moderate TEAE of transaminase increased. Lab results showed mild elevations starting on Day 8 (Alanine transaminase [ALT] 77 U/L, Aspartate aminotransferase [AST] 35 U/L, Total bilirubin 0.2 mg/dL), worsening on Day 16 (ALT 107 U/L, AST 35 U/L, Total bilirubin 0.47 mg/dL), then normalizing by Day 28. Levels rose again on Day 147 (ALT 157 U/L, AST 57 U/L, Total bilirubin 0.35 mg/dL) and peaked on Day 252 (ALT 208 U/L, AST 63 U/L, Total bilirubin 0.64 mg/dL). Three unscheduled follow-ups showed a downward trend, with final levels at ALT 65 U/L, AST 39 U/L, and Total bilirubin 0.47 mg/dL.

No relevant medical history or concurrent TEAE was reported. The TEAE was considered recovering/resolving. The investigator deemed the study drug unrelated to the TEAE, and no additional action was taken. Concomitant medication review revealed no suspicious agents.

No other clinically significant liver enzyme shifts were reported in patients receiving RGB-14-P or RGB-14-X in Studies RGB-14-001 or RGB-14-101. Hence, even though transiently elevated transaminases were observed in one patient treated with RGB-14, there is no evidence suggesting that treatment with RGB-14 is associated with a greater risk of hepatotoxicity compared to US-Prolia.

Injection Site Reactions (ISRs)

Study RGB-14-001

Local tolerance at the injection site was evaluated by the investigator or designee pre-dose, and 1, 8, and 24 hours post-dose. Severity was graded based on pain, tenderness, erythema, and induration (Table 35). Any injection site reaction was documented as an AE.

Table 35: Grading of Severity of Injection Site Reactions, Study RGB-14-001

Local reaction to injectable product	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially life-threatening)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24	Any use of narcotic pain reliever or	Emergency room visit or hospitalization

Local reaction to injectable product	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially life-threatening)
		hours or interferes with activity	prevents daily activity	
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/redness	2.5 to 5.0 cm	5.1 to 10.0 cm	> 10.0 cm	Necrosis or exfoliative dermatitis
Induration/swelling	2.5 to 5.0 cm and does not interfere with activity	5.1 to 10.0 cm or interferes with activity	> 10.0 cm or prevents daily activity	Necrosis

Source: reproduced from the Applicant's table 8-1 in the protocol, page 90

Injection site reaction TEAEs were reported in 3 (3.6%) patients in the RGB-14-X group (with preferred terms including injection site pain in 2 patients and injection site reaction in 1 patient). However, one of these patients reported the TEAE on Day 191 so the event was unlikely to be related to the study drug. Injection site reaction TEAEs were reported in 2 (2.4%) patients in the US-Xgeva group (with preferred terms including injection site bruising and injection site discoloration, one patient each). All were mild and non-serious events that did not lead to study discontinuation.

Study RGB-14-101

Skin examination was done by the investigator pre-dose and 1 hour post-dose on the day of and 1 week after each injection. Severity was graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5 (Table 36). Injection site reactions with a grading of ≥1 was recorded as an AE.

Table 36: Grading of Severity of Injection Site Reactions, Study RGB-14-101

Grade	Reactions
Grade 1	Tenderness with or without associated symptoms (e.g. warmth, erythema, itching)
Grade 2	Pain, lipodystrophy, edema, phlebitis
Grade 3	Ulceration or necrosis, severe tissue damage, operative intervention indicated
Grade 4	Life-threatening consequences, urgent intervention indicated
Grade 5	Death

Source: reproduced from the Applicant's table 8-1 in the protocol, page 63

Main Period

No injection site reactions occurred in the RGB-14-P group. In the US-Prolia group, one patient experienced mild injection site erythema and another mild injection site rash. Both events were non-serious.

Transition Period

In transition period, 3/62 (4.8%) patients from US-Prolia to RGB-14-P group experienced injection site reactions: one case of erythema and two cases of urticaria. In the US-Prolia to US-Prolia group, 1/63 (1.6%) patient reported injection site hematoma. No injection site reactions occurred in patients from RGB-14-P to RGB-14-P group. All reported events were mild and non-serious.

Hypersensitivity Reactions

The clinical reviewer searched the safety dataset for adverse event preferred terms coding to the Anaphylaxis OND Custom Medical Query (OCMQ) and Hypersensitivity Reaction OCMQ to evaluate for events of anaphylaxis and hypersensitivity in the clinical studies.

The Applicant utilized hypersensitivity narrow Standardized MedDRA Query (SMQ) to assess hypersensitivity reactions, which encompassed a range of nonspecific events, including allergic conjunctivitis and allergic rhinitis. Narratives were provided for all identified events. The following discussion focuses on events assessed by the investigators as related to the study drug and excludes injection site reactions previously discussed.

Study RGB-14-001

There were no events of anaphylaxis or hypersensitivity during this study, as determined by a search of the safety dataset for adverse event preferred terms coding to the Anaphylactic Reaction and Hypersensitivity Reaction OCMQ.

The Applicant identified one patient each from RGB-14-X group and US-Xgeva group with preferred term of rash according to the narrow SMQ search. However, these events occurred at least 17 days after the study drug administration. Therefore, they are both considered unlikely to be related to the study drug.

Study RGB-14-101

Main Period

Anaphylactic Reaction and Hypersensitivity Reaction OCMQ search did not identify any events in the Main Period.

The Applicant identified 3 patients each from RGB-14-P group (with preferred terms: dermatitis allergic rash papular, and eczema) and US-Prolia group (with preferred terms: rash pruritic, swelling of eyelid, and dermatitis allergic) through a narrow SMQ search. Analysis of the reported terms revealed that all events except one occurred at locations unrelated to the injection site (e.g., legs or hands). A single event described an "allergic reaction on the right arm area," although it did not explicitly indicate an injection

site reaction. Moreover, all events were non-serious and either mild or moderate in severity, and none of the patients tested positive anti-drug antibodies throughout the study. Therefore, the causality of these events to the study drug is difficult to establish.

Transition Period

A single mild and non-serious event of hypersensitivity occurred in one patient who continued US-Prolia. The reported term was “inhalant allergy unknown” and the event occurred 35 days after the third US-Prolia injection. No hypersensitivity events were observed in either the US-Prolia to RGB-14-P group or the RGB-14-P to RGB-14-P group according to the OCMQ search. Additionally, there were no events of anaphylaxis in any group based on the OCMQ search. The Applicant's search did not identify any additional events. Therefore, there is no evidence to suggest that transitioning from US-Prolia to RGB-14-P is associated with an increase in hypersensitivity reactions.

Fractures

Study RGB-14-001

No fractures were reported in this study.

Study RGB-14-101

Lateral thoraco-lumbar spine radiographs were obtained during the initial screening, at the conclusion of the Main Period (Week 52), and upon completion of the Transition Period (Week 78). All lateral spine radiographs were centrally read. Radiographs conducted to assess non-vertebral fractures were interpreted locally. Any fracture, regardless of symptoms, that occurred during the study was documented as an AE.

Main Period

During the Main Period, a slightly higher proportion of patients reported non-vertebral and vertebral fractures in the US-Prolia group (8 [3.5%] patients with vertebral and 10 [4.3%] patients with non-vertebral fractures) compared to the RGB-14-P group (5 [2.1%] patients with vertebral and 4 [1.7%] patients with non-vertebral fractures) (Table 37). None of the fracture events led to change in study treatment or study discontinuation.

Among the non-vertebral fractures, three events were classified as severe. These included one foot fracture and one humerus fracture in the RGB-14-P group, and one radius fracture in the US-Prolia group. The humerus and radius fractures were additionally categorized as serious events, as they necessitated hospitalization of the affected patients (refer to Section 6.3.2 for serious event narratives).

All vertebral fractures from both groups were non-serious and mild or moderate in severity.

Table 37: N(%) of patients experiencing Treatment Emergent Adverse Events of Fracture, Main Period, Study RGB-14-101

	RGB-14-P (N=242)	US-Prolia (N=231)
Patients with Fractures, n (%)	9 (3.7)	18 (7.8)
Ankle fracture[a]	0	1 (0.4)
Foot fracture	2 (0.8)	1 (0.4)
Forearm fracture	0	1 (0.4)
Hand fracture	0	1 (0.4)
Humerus fracture	1 (0.4)	1 (0.4)
Lower limb fracture[a]	0	1 (0.4)
Lumbar vertebral fracture	2 (0.8)	1 (0.4)
Radius fracture	0	1 (0.4)
Rib fracture	0	2 (0.9)
Spinal compression fracture	2 (0.8)	0
Spinal cord compression	0	1 (0.4)
Thoracic vertebral fracture	1 (0.4)	6 (2.6)
Tooth fracture	1 (0.4)	2 (0.9)

Source: clinical reviewer analysis
[a] These events occurred at concurrently in one patient.

Transition Period

Non-vertebral fractures were overall rare and reported in one patient each from RGB-14-P to RGB-14-P and US-Prolia to US-Prolia group, and none from US-Prolia to RGB-14-P group. Vertebral fractures were reported in three patients each from RGB-14-P to RGB-14-P group and US-Prolia to RGB-14-P group, and one patient from US-Prolia to US-Prolia group (Table 38). All fractures were mild or moderate in severity and none were serious.

Table 38: N(%) of patients experiencing Treatment Emergent Adverse Events of Fracture, Transition Period, Study RGB-14-101

	RGB-14-P to RGB-14-P (N=63)	US-Prolia to RGB-14-P (N=62)	US-Prolia to US-Prolia (N=63)
Patients with Fractures, n (%)	4 (6.3)	3 (4.8)	1 (1.6)
Foot fracture[a]	0	0	1 (1.6)
Forearm fracture	1 (1.6)	0	0
Lumbar vertebral fracture	1 (1.6)	2 (3.2)	0
Spinal cord compression	0	1 (1.6)	0
Thoracic vertebral fracture[a]	2 (3.2)	0	1 (1.6)

Source: clinical reviewer analysis
[a] One patient (RGB-14-101-34050002) in US-Prolia to US-Prolia group experienced foot and thoracic vertebral fractures at different times during the Transition Period.

Three patients who switched from US-Prolia to RGB-14-P and one patient who continued US-Prolia experienced fractures during the Transition period. This small difference in fracture incidence is unlikely to represent a clinically meaningful difference between the study drugs or when transitioning from US-Prolia to RGB-14-P.

Osteonecrosis of the jaw

Osteonecrosis of the jaw is identified as a potential adverse reaction under the Warnings and Precautions section of the USPI for Prolia. No patients in either studies had a TEAE of osteonecrosis of the jaw.

Pregnancy

In Study RGB-14-001, one patient who received RGB-14-X 60 mg reported that his female partner became pregnant. The pregnancy was confirmed by a positive test on Day 97. At approximately 37 weeks gestation, the patient provided an update, indicating that there were no abnormalities on antenatal check-ups, no complications during the pregnancy, and no usage of concomitant medications. Unfortunately, subsequent attempts by the Applicant to contact the patient were unsuccessful. As a result, further information regarding the outcome of the pregnancy is unavailable.

No pregnancy was reported in Study RGB-14-101.

6.4. Clinical Conclusions on Immunogenicity

The assessment of immunogenicity occurred in the comparative pharmacokinetic Study RGB-14-001 and the comparative clinical Study RGB-14-101. There was no meaningful difference between the treatment arms in either study with respect to development of anti-drug antibodies (ADAs) or neutralizing antibodies (NAbs). Furthermore, presence of ADAs or Nabs had no apparent impact on efficacy or safety outcomes. Refer to Section 5.4 for complete details of the immunogenicity assessment and conclusions from the Clinical Pharmacology review team.

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6.5. Risk in Terms of Safety or Diminished Efficacy of Switching Between Products and the Any Given Patient Evaluation (to Support a Demonstration of Interchangeability)

The Applicant's development program established that RGB-14-P, US-Prolia, RGB-14-X, and US-Xgeva, share identical primary structures and comparable secondary and tertiary structures. Functional assays showed similarity between RGB-14-P, US-Prolia, RGB-14-X, and US-Xgeva with respect to pharmacologic activity. There were no

meaningful differences in pharmacokinetics between RGB-14-X and US-Xgeva in the PK similarity study.

The comparative clinical study showed no meaningful difference in PK, efficacy, safety, or immunogenicity between RGB-14-P and US-Prolia in the treatment of post-menopausal women with osteoporosis. Presence of ADAs had no impact on PK, efficacy, or safety. Although some numerical differences were observed between RGB-14-P and US-Prolia in terms of incidences of certain adverse events, the absolute differences were not large and not considered clinically meaningful. Importantly, the adverse event profile of both products was comparable.

A transition from US-Prolia to RGB-14-P was well tolerated with no meaningful impact on PK, efficacy, or safety. At six months post-transition (i.e., Month 19), the percentage change from baseline in lumbar spine BMD was comparable in the two treatment groups. There was no meaningful increase in ADA titers or incidence of NAbs after transitioning from US-Prolia to RGB-14-P.

The Applicant provided sufficient justification that RGB-14-P and RGB-16-X can be expected to produce the same clinical result as US-Prolia and US-Xgeva, respectively, in any given patient. The scientific justification considered the following issues that are described in the FDA guidance for industry, Considerations in Demonstrating Interchangeability with a Reference Product.

Mechanism of Action

Across all approved indications for US-Prolia and US-Xgeva, the clinical efficacy is based on denosumab binding to RANKL and prohibiting its binding to the RANK receptor. Functional assays established that RGB-14-P and RGB-14-X exhibit the same pharmacologic activity as US-Prolia and US-Xgeva and has identical primary structure to US-Prolia and US-Xgeva. Furthermore, there was no clinically meaningful difference in the effect of RGB-14-P and US-Prolia on the serum bone turnover marker CTX and lumbar spine bone mineral density, which further supports a shared mechanism of action.

The Applicant provided adequate justification to support that RGB-14-P and RGB-14-X have the same, known, and potential mechanisms of action, as US-Prolia and US-Xgeva for each indication for which US-Prolia and US-Xgeva are licensed.

Pharmacokinetics

The applicant provided adequate justification that RGB-14-P and RGB-14-X are expected to have a similar PK profile as US-Prolia and US-Xgeva for each indication for which US-Prolia and US-Xgeva are licensed.

Immunogenicity

In the RGB-14-P and RGB-14-X development program, immunogenicity was evaluated in populations considered sensitive for detecting clinically meaningful differences:

female subjects with post-menopausal osteoporosis (PMO) and healthy subjects. Immunogenicity was found to be similar when comparing RGB-14-X and US-Xgeva in the PK Similarity Study, RGB-14-001 in healthy subjects, and between RGB-14-P and US-Prolia in the comparative clinical study, Study RGB-14-101. The Applicant provided adequate justification that RGB-14-P and RGB-14-X are expected to have a similar immunogenicity as US-Prolia and US-Xgeva for each indication for which US-Prolia and US-Xgeva are licensed.

Toxicity

Comparative safety was assessed in the comparative clinical study RGB-14-101, which was conducted in female subjects with PMO. Supportive safety information was also available from the PK similarity study, Study RGB-14-001. The Applicant provided adequate justification that RGB-14-P and RGB-14-X are expected to have a similar safety profile as US-Prolia and US-Xgeva for each indication being sought for licensure.

The Applicant also provided sufficient scientific justification that the risk in terms of safety or diminished efficacy of alternating or switching between use of RGB-14-P and US-Prolia, or use of RGB-14-X and US-Xgeva, is not greater than the risk of using US-Prolia or US-Xgeva without such alternation or switch. The Applicant referenced the comparative analytical data provided in their application that evaluated and compared critical quality attributes of RGB-14-P and RGB-14-X and US-Prolia and US-Xgeva and the results from the comparative clinical study (RGB-14-P) to support their justification. The Applicant also described that the results from the single transition included in Study RGB-14-P provided supportive evidence of a low immunogenic risk and no safety concerns with switching between RGB-14-P and RGB-14-X and US-Prolia or US-Xgeva.

FDA considers the risk of a clinically impactful immunogenic response when alternating or switching between RGB-14-P and RGB-14-X, and US-Prolia or US-Xgeva, respectivly to be low. Thus, a switching study that compares immunogenicity and PK and/or PD to assess whether there could be diminished efficacy or safety issues associated with alternating or switching between use of RGB-14-P and US-Prolia, or use of RGB-14-X and US-Xgeva, was considered unnecessary to support a demonstration of interchangeability for RGB-14.

Conclusion

In summary, the data and information provided by the Applicant are sufficient to demonstrate that RGB-14-P and RGB-14-X can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient and that the risk, in terms of safety or diminished efficacy of alternating or switching between use of RGB-14-P and US-Prolia, or RGB-14-X and US-Xgeva, is not greater than the risk of using US-Prolia or US-Xgeva without alternation or switch.

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6.6. Extrapolation

6.6.1. Division of General Endocrinology and Office of Oncology Drugs

The Applicant submitted data and information in support of a demonstration that RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between RGB-14-P and US-Prolia, or RGB-14-X and US-Xgeva, in terms of safety, purity, and potency. In addition, the totality of evidence submitted in the application sufficiently demonstrates that RGB-14-P and RGB-14-X can be expected to produce the same clinical result as US-Prolia and US-Xgeva, respectively in any given patient and that, the risk in terms of safety or diminished efficacy of alternating or switching between use of RGB-14-P and US-Prolia, or RGB-14-X and US-Xgeva, is not greater than the risk of using US-Prolia or US-Xgeva without such alteration or switch.

The Applicant is seeking licensure of RGB-14-P and RGB-14-X for the following indication(s) for which US-Prolia and US-Xgeva have been previously licensed and for which RGB-14-P and RGB-14-X have not been directly studied:

- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer
- 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 Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of RGB-14-P and RGB-14-X as interchangeable biosimilars for each such indication for which licensure is sought and for which US-Prolia and US-Xgeva have been previously approved.

Therefore, the totality of the evidence provided by the Applicant supports licensure of RGB-14-P and RGB-14-X as biosimilar to and interchangeable with US-Prolia and US-Xgeva, respectively for each of the following indication(s) for which the Applicant is seeking licensure of RGB-14-P and RGB-14-X and for which US-Prolia and US-Xgeva have been previously approved:

- Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for prostate cancer.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.
- 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.

Conclusions

The Division of General Endocrinology and the Office of Oncology Drugs 1 conclude that the Applicant has provided sufficient scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity and toxicity profile) for extrapolation of the data and information submitted in the application to support licensure of RGB-14-P and RGB-14-X for all indications for which US-Prolia and US-Xgeva are licensed, respectively.

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7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, denosumab-qbde, was found to be conditionally accepted by the Agency. Refer to the Division of Medication Error Prevention and Analysis 1 (DMEPA 1) review dated June 27, 2025, in DARRTS.

7.2. Proprietary Name

The proposed proprietary names for denosumab-qbde are conditionally approved as Enoby (denosumab- qbde 60 mg/mL prefilled syringe) and Xtrenbo (denosumab- qbde 120 mg/1.7 mL vial). These names have been reviewed by DMEPA 1, who concluded the names are acceptable. Refer to reviews dated November 6, 2024 and November 14, 2024 in DARRTS.

7.3. Other Labeling Recommendations

The Prescribing Information (PI) review includes a summary of the rationale for major changes incoportated into the finalized PI as compared to the Applicant's draft submitted on September 27, 2024. The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare provider.

For Enoby, edits were made throughout the PI to align with the reference product Prolia S-219 approved May 22, 2025, and language used when referring to a biosimilar to US-Prolia. "Enoby", "denosumab-qbde", "denosumab", or "denosumab products" were used in place of Prolia as applicable.

For Enoby, in addition to aligning with Prolia S-219, the following product specific edits are included in the draft Prescribing Information:

- 2 DOSAGE AND ADMINISTRATION/ 2.4 Preparation and Administration: removed (b) (4) from the sentence "Do not use if the solution is discolored or cloudy or if the solution contains (b) (4) particles or foreign particulate matter" because Enoby does not contain visible particles based on the evaluation of the proposed drug product.
- 2 DOSAGE AND ADMINISTRATION/ 2.4 Preparation and Administration: deleted figure showing subcutaneous injection at 45 to 90 degree angles and disposal of used needle in sharps container because the figures show administration information familiar to healthcare providers or are already noted in text.

- 3 DOSAGE FORMS AND STRENGTHS: solution characteristics described as “clear to slightly opulescent, colorless to pale yellow” as confirmed by product quality reviewer.
- 11 DESCRIPTION: updated (b) (4) to “glacial acetic acid” per product quality reviewer, inactive ingredients listed in alphabetical order, and inactive ingredients listed by amounts (mg), not percentage (%).
- 16 HOW SUPPLIED/STORAGE AND HANDLING/ How Supplied: included statement “The prefilled syringe is not made with natural rubber latex” as confirmed by product quality reviewer.

For Xtrenbo, edits were made throughout the PI to align with the reference product Xgeva S-222 approved May 30, 2025, and language used when referring to a biosimilar to US-Xgeva. “Xtrenbo”, “denosumab-qbde”, “denosumab”, or “denosumab products” were used in place of Xgeva as applicable.

For Xtrenbo, in addition to aligning with Xgeva S-222, the following product specific edits are included in the draft Prescribing Information:

- 2 DOSAGE AND ADMINISTRATION/ 2.5 Preparation and Administration: removed (b) (4) from the sentence “Do not use if the solution is discolored or cloudy or if the solution contains (b) (4) particles or foreign particulate matter” because Xtrenbo does not contain visible particles based on the evaluation of the proposed drug product.
- 3 DOSAGE FORMS AND STRENGTHS: solution characteristics described as “clear to slightly opulescent, colorless to pale yellow” as confirmed by product quality reviewer.
- 11 DESCRIPTION: updated (b) (4) to “glacial acetic acid” per product quality reviewer, and inactive ingredients listed by amounts (mg), not percentage (%).
- 16 HOW SUPPLIED/STORAGE AND HANDLING/ included recommendation “Avoid vigorous shaking of Xtrenbo” as confirmed by product quality reviewer.

Authors:

LaiMing Lee, PhD
Associate Director for Labeling, DGE

Shivangi Vachhani, MD
Cross Discipline Team Leader, DGE

8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications

were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 14.1 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

Authors:

Sooyoung Lim
Clinical Reviewer

Shivangi Vachhani, MD
Cross Disciplinary Team Leader

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

Author:

Sooyoung Lim M.D.
Clinical Reviewer

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a “new active ingredient” for purposes of PREA.

At the time of this review, other denosumab products, Jubbonti and Wyost, have been approved as interchangeable biosimilars and have qualified for FIE. RGB-14 will be approved as a biosimilar product, as discussed in Section 1.7, and therefore is considered to have a new active ingredient for the purposes of PREA. The Applicant submitted the initial Pediatric Study Plan (iPSP) on March 31, 2021, and an agreement letter was issued on July 21, 2022.

For the following indications and populations, PREA requirements were either waived for, or inapplicable to US-Prolia or US-Xgeva, and therefore the Applicant is not required to submit a pediatric assessment for them:

Prolia:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture,
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture,
- Treatment 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, and
- Treatment of glucocorticoid-induced osteoporosis in pediatric patients aged 0 to <5 years of age at high risk for fracture.

Xgeva:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of hypercalcemia of malignancy of refractory to bisphosphonate therapy
- Treatment of pediatric patients who are not skeletally mature with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

The applicant submitted a pediatric assessment for giant cell tumor of the bone that is unresectable or where surgical resection is likely to result in severe morbidity in skeletally mature adolescents (aged 12 to 17 years) based on a demonstration of biosimilarity and providing adequate scientific justification to support extrapolation of data and information to support licensure. Refer to Section 6.6 for review of the assessment.

The Applicant initially requested to defer the submission of the pediatric assessment for the glucocorticoid-induced osteoporosis indication in pediatric patients aged 5 to 17 years, pending the availability of pediatric data from US-Prolia. However, on May 22, 2025, US-Prolia (BLA 125320/S-219) updated the labeling without approving the pediatric indication. Specifically, appropriate pediatric language has been added to Subsection 8.4 Pediatric Use of Section 8 USE IN SPECIFIC POPULATIONS of the US-Prolia labeling to reflect that safety and effectiveness were not established in the phase 3 clinical trial evaluating the effect of denosumab on glucocorticoid-induced osteoporosis in children aged 5 to 17 years old. Accordingly, the Applicant fulfilled PREA requirements for this indication by including the relevant pediatric information in RGB-14-P labeling.

PeRC discussed this application on July 29, 2025, and concurred with the Division's recommendations.

Authors:

Sooyoung Lim M.D.
Clinical Reviewer

Shivangi Vachhani, MD
Cross Disciplinary Team Leader

11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

US-Prolia is approved with a REMS to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients. The most recent modification to the Prolia REMS was approved on March 5, 2024. The Prolia REMS consists of a communication plan (CP) and timetable for submission of assessments.

On September 27, 2024, the Applicant submitted a BLA with a proposed REMS for Enoby that consisted of a CP and timetable for submission of assessments. The Agency sent comments to the Applicant on March 22, 2025, and August 5, 2025. The Applicant submitted amendments on April 17, 2025, and August 12, 2025, in response to the Agency's comments.

The Division of Risk Management (DRM) reviewed the amended REMS and found the Enoby REMS, as submitted on August 12, 2025, acceptable. The Enoby REMS is comparable to the US-Prolia REMS and is designed to communicate the same key risk messages and achieve the same level of patient safety.

The Enoby REMS goal and objective are:

> The goal of the Enoby REMS is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Enoby. The following describes the objective associated with the REMS:
>
> Objective 1: Inform healthcare providers on:
>
> - Risk of severe hypocalcemia in patients with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m^2)
> - Need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Enoby in patients with advanced chronic kidney disease

The Enoby REMS elements consist of a CP and timetable for submission of assessments.

The CP elements include:

- REMS Letter to Healthcare Providers
- REMS Letter to Professional Societies
- Patient Guide
- REMS Website

Timetable for submission of assessments is at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS. The Enoby REMS assessment plan was

reviewed by the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) and found to be acceptable.

Authors:

Christopher Booze, PharmD
Risk Management Analyst, DRM

Yasmeen Abou-Sayed, PharmD
Team Leader, DRM

11.2. Recommendations for Postmarket Requirements and Commitments

Not applicable

Authors:

Shivangi Vachhani, MD
Cross Disciplinary Team Leader, DGE

12. Comments to Applicant

Not applicable

13. Division Director Comments

13.1. Division Director (OND – Clinical) Comments

I concur with the review team's assessment of the data and information submitted in this BLA. The data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrate that RGB-14-P and RGB-14-X are biosimilar to US-Prolia and US-Xgeva, respectively. I also concur with the team's recommendation to provisionally determine that RGB-14-P and RGB-14-X meet the standards for interchangeability under section 351(k)(4) of the PHS Act. We have not identified any deficiencies that would justify a complete response action. Although we have provisionally determined that RGB-14-P and RGB-14-X meet the requirements for licensure as interchangeable biosimilar product, pursuant to section 351(k)(6) of the Public Health Service Act, we are unable to make such a determination because of unexpired first interchangeable exclusivity for US-licensed Jubbonti and Wyost, as discussed in Section 1.7 above. Accordingly, I also concur with the review team's recommendation to provisionally determine that:

- RGB-14-P, 60 mg/mL injection for SC use in a single-dose PFS meets the applicable standards for interchangeability with US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS

- RGB-14-X, 120 mg/1.7 mL injection for SC use in a single-dose vial meets the applicable standards for interchangeability with US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial

These RGB-14 products have met the statutory interchangeability requirements for the following indications for which US-Prolia and US-Xgeva have previously been approved and for which the applicant is seeking licensure:

U.S.-Prolia:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

U.S.-Xgeva:

- 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

When action is taken for this BLA, it will be administratively split to facilitate an approval action for RGB-14-P and RGB-14-X as biosimilar products (“Original 1”) and a provisional determination that RGB-14-P and RGB-14-X are interchangeable biosimilar products, as described in Section 1.7 above (“Original 2”). The Applicant is expected to submit an amendment seeking approval of BLA 761439/Original 2 no more than six

months prior to the expiration of exclusivity, or when the Applicant believes that BLA 761439/Original 2 will become eligible for approval.

Author:
Theresa Kehoe, MD
Division Director, Division of General Endocrinology

14. Appendices

14.1. Financial Disclosure

Covered Clinical Study RGB-14-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study RGB-14-101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 37		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.2. Clinical Pharmacology Appendices

14.2.1. Summary of Bioanalytical Method Validation and Performance

Bioanalytical assays were developed and validated for the determination of study drug serum concentration as well as serum sCTX/CTX1 levels. The assays and their application in the clinical studies are summarized in Table 39.

Table 39. Summary of the bioanalytical assays

Method ID	Method title	Analyte	Applicable clinical studies
GLP2015 (Section 1.5.1)	An electrochemiluminescent method for the quantitative determination of denosumab (RGB-14 and Xgeva) in human serum	Denosumab	RGB-14-001 RGB-14-101
GLP2229 (Section 1.5.2)	Bioanalytical method for detection of anti-denosumab antibodies from human serum	Anti-denosumab antibodies	RGB-14-001 RGB-14-101
GLP2114	Bioanalytical method for detection of anti-denosumab antibodies from human serum	Anti-denosumab antibodies	Not used
GLP2226 (Section 1.5.3)	Bioanalytical method for detection of neutralizing anti-denosumab antibodies from human serum	Neutralizing anti-denosumab antibodies	RGB-14-101
1-P-PR-PRO-9000437 (Section 1.5.4)	Electrochemiluminescence (ECLIA) assay for the analysis of CTX1 in human serum	CTX1	RGB-14-101
1-P-PR-PRO-9000436 (Section 1.5.5)	Electrochemiluminescence (ECLIA) assay for the analysis of P1NP in human serum	P1NP	RGB-14-101
SCH-AU-STU-ASS-0229-00 (Section 1.5.6)	Bioanalytical method for determination of sCTX concentration in serum	sCTX	RGB-14-001

Note: Different nomenclature was used in the Phase I and Phase III studies regarding the pharmacodynamic marker (sCTX/CTX1)

This section has included the review of method validation and performance for quantifying study drug and sCTX serum concentrations. Refer to OPQA3's review for an assessment of the bioanalytical method validation and performance of the ADAs/NAbs assays.

Pharmacokinetics

Quantification of serum study drug concentration

- **Method validation**

Analytical Validation Report	GLP2015
Location	5.3.1.4
This analytical method was used in the following studies:	RGB-14-001 (bioanalysis internal code: (b) (4) RGB-14-101 (bioanalysis internal code:
Analyte Location of product certificate	Denosumab (RGB-14-X, RGB-14-P, Xgeva, Prolia) Appendices in bioanalytical reports
Methodology	Bridging immunoassay with ECL detection, MSD Meso QuickPlex SQ 120
Biological matrix	Human serum
Assay MRD	10-fold
Calibration concentrations (ng/ml)	0.42 (low anchor), 1.00; 2.40; 5.76; 13.83; 33.18; 79.64; 191.13; 458.71; 1100.90 (high anchor2); 2642.16 (high anchor1)
Lower limit of quantification (ng/ml)	1.00 ng/mL for normal and female osteoporosis serum 1.50 ng/mL for lipemic and haemolysed samples
QC concentrations (ng/ml)	LLOQ 1.00; LQC 2.80; MQC 32.00; HQC 345.00; ULOQ 458.4
Sample storage	At nominal -80°C (recommended) or -20°C
Sample volume	15 µL

Validation parameters		Results			
		RGB-14-X		Xgeva	
		Intra-run	Inter-run	Intra-run	Inter-run
Accuracy (bias %)	LLOQ (1 ng/mL)	-18.0 – 18.0	-5.0	-18.0 – 18.0	-5.0
	LQC (2.8 ng/mL)	-18.9 – 17.1	-2.9	-15.4 – 19.3	-1.1
	MQC (32 ng/mL)	-13.0 – 8.3	-2.0	-13.8 – 15.2	-1.0
	HQC (345ng/mL)	3.5 – 11.5	6.7	2.0 – 17.5	10.8
	ULOQ (458.4 ng/mL)	1.6 – 11.4	4.7	0.6 – 16.9	8.5
Precision (CV %)	LLOQ (1 ng/mL)	2.3 – 3.7	14.7	1.0 – 4.6	13.7
	LQC (2.8 ng/mL)	0.9 – 2.3	12.5	1.0 – 5.5	12.3
	MQC (32 ng/mL)	1.7 – 4.7	8.3	1.0 – 5.0	10.7
	HQC (345ng/mL)	0.0 – 5.4	4.0	0.3 – 7.2	5.8
	ULOQ (458.4 ng/mL)	0.6 – 8.4	4.9	0.3 – 8.2	6.6
Total error (TE %)	LLOQ (1 ng/mL)	11.7 – 21.7	19.7	6.0 – 20.5	18.7
	LQC (2.8 ng/mL)	4.4 – 19.8	15.4	6.9 – 21.1	13.3
	MQC (32 ng/mL)	4.3 – 17.3	10.3	4.8 – 16.2	11.8
	HQC (345ng/mL)	5.5 – 14.8	10.8	2.3 – 21.7	16.6
	ULOQ (458.4 ng/mL)	3.1 – 16.1	9.6	0.9 – 18.5	15.1

Dilution linearity	(bias %)	Dilution factor 30	1.7	-3.9	-4.1	-6.0
		Dilution factor 50	-1.9	-4.4	-5.3	-7.0
		Dilution factor 100	-10.4	-9.8	-9.4	-11.0
	(CV%)	Dilution factor 30	3.4	6.6	2.2	1.7
		Dilution factor 50	2.9	2.3	3.6	3.5
		Dilution factor 100	4.6	8.2	2.1	2.0
		Overall precision	6.1		3.3	
Specificity against	Osteoprotegerin		Bias: -12.0% at LLOQ 4.4% at ULOQ		Bias: -20.0% at LLOQ 5.0% at ULOQ	
	RANKL		Bias: -5.0% at LLOQ 6.8% at ULOQ		Bias: -19.0% at LLOQ 12.7% at ULOQ	
	25(OH)-D3		Bias: -13.0% at LLOQ 4.9% at ULOQ		Bias: -13.0% at LLOQ 8.6% at ULOQ	
Selectivity	blanks (all types)		BLQ for all 46 lots of individual matrices			
	normal human serum		100 % acceptable at HQC 90% acceptable at LLOQ		95% acceptable at HQC 90% acceptable at LLOQ	
	lipemic human serum		100% acceptable at HQC 100% acceptable at 1.5 ng/mL		100% acceptable at HQC 100% acceptable at 1.5 ng/mL	
	haemolysed human serum		100% acceptable at HQC 100% acceptable at 1.5 ng/mL		100% acceptable at HQC 100% acceptable at 1.5 ng/mL	
	osteoporosis female serum		100% acceptable at HQC 100% acceptable at LLOQ		100% acceptable at HQC 100% acceptable at LLOQ	
Hook effect			No up to 10000 ng/mL for both analytes			
	blocking time		60-131 mins			

Validation parameters		**Results**	
		RGB-14-X	**Xgeva**
Robustness of	incubation time with samples	60-138 mins	
	incubation time with detection reagent	60-120 mins	
	manual plate washing	acceptable	
Short-term room temperature stability in serum		Demonstrated for 48 hours at RT (both analytes)	
Freeze and thaw stability in serum		Demonstrated for 5 cycles (from RT to -80°C)	
Blood stability (clotting time)		Demonstrated from 10 minutes to 6 hours at RT (tested for RGB-14)	
RGB-14-X stock solution stability		Up to 461 days (15.2 months) at +5°C in aliquots	
Xgeva stock solution stability		Up to 461 days (15.2 months) at +5°C in aliquots	
RGB-14-X working solution stability		Up to 461 days (15.2 months) at -80°C in aliquots	
Xgeva working solution stability		Up to 155 days (5 months) at -80°C in aliquots	

Long-term stability	Up to 743 days (24.4 months) at -20°C Up to 832 days (27.4 months) at -80°C in serum for both analytes
Bioanalytical comparability	The method is valid for the quantification of both analytes
Parallelism	Proved for 6 individual samples from RGB-14-001 clinical study containing RGB-14-X or Xgeva at C_{max} concentration

Source: Summary of biopharmaceutics, table 6 and 7

- **Method performance**

Accuracy and Precision of study drug Standards and QC Samples for Method 1

	Accuracy (% Deviation)		Precision (% CV)	
	Standards	QC Samples	Standards	QC Samples
RGB-14-001	within ± 3.9	within ± 4.7	≤ 3.9	≤ 6.6
RGB-14-101	within ± 4.5	within ± 2.9	≤ 3.9	≤ 8.6

Storage period of study samples

Study ID and analyte	Longest storage period
RGB-14-001, denosumab	631 days at temperature -80°C
RGB-14-101, denosumab	<832 days at temperature -80°C

Sample analysis statistics

Study ID	RGB-14-001	RGB-14-101
Analyte	Denosumab	Denosumab
Total numbers of collected samples	4704	3713
Total numbers of samples with valid results	4704	3712
Total numbers of reassayed samples[1,2]	131	181
Total number of analytical runs[1]	175	141
Total number of valid analytical runs [1]	172	139
Incurred sample reanalysis		
Number of samples	286	240
Percentage of samples where the difference between the two values was less than 30%	98.95 %	99.17 %

[1] *Without incurred sample*

[2] *Due to other reasons than not valid run*

Reviewer Comments:
The acceptance criteria and performance of the bioanalytical method to determine study drug concentration in human serum are in compliance with the Agency's Bioanalytical Method Validation Guidance. Study samples were analyzed within the stability period. Therefore, the performance of the bioanalytical method to determine study drug concentration in clinical studies are acceptable.

Pharmacodynamics

Serum carboxy terminal cross-linking telopeptide of type I collagen (s-CTX) was quantified in both studies RGB-14-001 and RGB-14-101.

Bioanalytical methods that were used to assess the PD biomarker(s) and/or the PD effect(s) of the study drug(s)

The Applicant utilized an electrochemiluminescence immunoassay (ECLIA) methods to quantify sCTX levels in human serum samples. The methods was based on commercially available diagnostic kits from Roche and performed on a Cobas E601/602 analyzer.

The sCTX assay used biotinylated monoclonal anti-β-CrossLaps antibodies and ruthenium-labeled β-CrossLaps-specific antibodies to form sandwich complexes that were subsequently detected via electrochemiluminescence. Although the diagnostic kit was validated by the original manufacturer Roche, an additional validation was performed.

Reviewer's Comments:

The bioanalytical method for sCTX appear to be appropriately validated with respect to precision and accuracy. Method performance during sample analysis was acceptable. However, an OSIS inspection conducted at (b) (4) *the bioanalytical laboratory that performed the sCTX analysis for Study RGB-14-001, identified the following issues:*

- *Quality control (QC) sample acceptance criteria: On four analysis dates (March 17, 2021, August 24, 2022, September 8, 2022, and September 21, 2022), high QC samples exceeded the acceptance criteria of ±*(b) (4)*% bias. The Applicant claims that although the high QC samples exceeded the acceptance criteria, they remained within the manufacturer's specified ranges.*

- *Data retention practices: The laboratory did not retain the raw electrochemiluminescence data from the Cobas 6000 instrument, though they maintained the final concentration results.*

- *Lower limit of quantitation: The sCTX concentration values were below the validated lower limit of quantitation (0.05 ng/mL), which is considered unreliable.*

Given these concerns, the PD evaluation for sCTX in Study RGB-14-001 was interpreted with caution in this review.

14.2.2. Other Clinical Pharmacology Information

Not Applicable.

14.3. Clinical Appendices

14.3.1. Schedule of Assessments, Study RGB-14-101

Figure 11: Schedule of Assessments, Study RGB-14-101, Main Period

Study Period	Days (weeks after first IMP administration)														
	Screening[b]	Treatment Period 1								Treatment Period 2[c]					
Day(s)[a] (Week)	-35 to 0 (-5 to 0)	1 (0)	8 (1)	15 (2)	30 (4)	60 (8)	90 (12)	120 (17)	150 (21)	1 (26)	8 (27)	15 (28)	30 (30)	90 (38)	183 (52)[c]/ EOS/ ET
Window Period (Days)			± 1	± 1	± 3	± 4	± 4	± 4	± 4	± 4	± 1	± 1	± 3	± 4	± 4
General Assessments															
Informed Consent	X														
Recording of Demographic Data	X														
Inclusion/Exclusion Criteria Assessment	X	X[d]													
Medical and Surgical History	X														
Weight, Height, BMI[e]	X	X[d]								X[d]					X
Randomisation		X[d]													
IMP Administration		X								X					
Pre-visit Phone Call[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Participant Identification and Visit Reminder Card[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments															
Physical Examination[h]	X	X[d]	X							X[c]					X
Haematology and Clinical Chemistry	X	X[d, i]	X	X[j]	X		X			X[d, i]	X	X[j]	X	X	X
HBV, HCV and HIV Screening	X														
Urinalysis[k]	X	X[d]								X[d]					X
12-lead ECG	X	X[d]								X[d]					X
Vital Signs[l]	X	X[m]	X	X	X	X	X	X	X	X[d]	X	X	X	X	X
Local Tolerance (Skin Examination)		X[n]	X							X[n]	X				
Prior and Concomitant Medication[o]	◄														►
Adverse Events	◄														►
Medical Device Events[p]		X								X					
Efficacy Assessment															
DXA Scan Assessment	X[q]									X[r]					X
Lateral Spine X-ray	X[q]														X

Study Period	Days (weeks after first IMP administration)														
	Screening[b]	Treatment Period 1								Treatment Period 2[c]					
Day(s)[a] (Week)	-35 to 0 (-5 to 0)	1 (0)	8 (1)	15 (2)	30 (4)	60 (8)	90 (12)	120 (17)	150 (21)	1 (26)	8 (27)	15 (28)	30 (30)	90 (38)	183 (52)[c]/ EOS/ ET
Window Period (Days)			± 1	± 1	± 3	± 4	± 4	± 4	± 4	± 4	± 1	± 1	± 3	± 4	± 4
Immunogenicity Assessment/Serum Drug Concentration Assessment															
Immunogenicity (binding ADAs and NAbs) Sampling		X[d]		X	X					X[d]		X	X		X[d]
Serum Drug Concentration Sampling		X[d]		X	X					X[d]		X	X		X[d]
PD															
PD (Serum CTX) Sampling[s]		X[d]	X	X	X	X	X	X	X	X[d]					X[d]
PD (Serum P1NP) Sampling[s]		X[d]			X					X[d]					X[d]

ADA = anti-drug antibody; BMI = body mass index; CTX = collagen C-telopeptide; DXA = dual energy x-ray absorptiometry; ECG = electrocardiogram; EOS = End-of-Study, ET = early termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IMP = investigational medicinal product; NAbs = neutralising antibodies; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic(s)

a. Day(s) refer to days within Screening or Treatment Period.
b. The Screening visit may be conducted over the Screening period (i.e., more than 1 day can be utilised for Screening during to the Screening period), if necessary, for logistical reasons.
c. Participants who will continue to receive the IMP during Treatment Period 3 will not have an End-of-Study visit on Week 52 but will proceed to Day 1 of Treatment Period 3 (Week 52), see Table 1-2. Please see Section 6.7 for additional information on the transition treatment for participants not continuing in Transition Period of study.
d. Procedure(s)/assessment/blood collection to be performed predose.
e. Height will be measured without shoes at Screening and at all timepoints when BMI is measured.
f. All participants will be contacted by phone 1 day prior to every visit for assessing coronavirus disease 2019 symptoms and signs and if they had any contact with a person who has tested positive for severe acute respiratory syndrome coronavirus 2. During the pre-visit call participants will be reminded of fasting conditions for blood analysis (as applicable).
g. At each visit participants will be provided with a participant identification and visit reminder card. The Investigator must update the visit reminder card at each visit with the details for the next visit.
h. A comprehensive physical examination will include an assessment of general appearance and a review of systems (head, eyes, ears, nose, mouth/oral cavity, throat/neck, thyroid, lymph nodes, dermatologic, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal and neurologic systems).
i. Additional local calcium testing predose may be performed according to local practice or at Investigator's discretion.
j. Albumin-adjusted serum calcium only.
k. Sites will perform a urine dipstick. In case of abnormal results, a urine sample may be sent to the central laboratory for full analysis if deemed necessary by the Investigator. See Appendix 2 (Section 10.2).
l. Vital signs include measurement of blood pressure, pulse and body temperature. Respiratory rate to be assessed at the discretion of the Investigator. Systolic and diastolic blood pressure and pulse measurements will be assessed after the participant has been sitting for at least 5 minutes with back supported and both feet on the floor.
m. Assessments to be done predose and 1 hour postdose.
n. Injection site reaction assessment should be done predose and approximately 1 hour postdose, during this 1 hour period (i.e., from dosing to the injection site assessment) the participant will stay in the clinic for general safety observation. Any further assessment of the injection site or prolonged observation of the participant may be done at the discretion of the Investigator.
o. Compliance with daily calcium and vitamin D intake will be monitored and assessed throughout the study.
p. Information on medical device events (e.g., needle broken, dose not administered properly, syringe condition problem) and medical device events (device incident/deficiency) that caused adverse events or events that led to serious adverse events are to be reported by unblinded site staff in the Product Complaint Form and electronic case report form (adverse events and serious adverse events only) as described in the Addendum to Investigator Manual and the Product Complaint Procedure. A medical device event related to Prolia® will qualify as a device incident and a medical device event related to RGB-14-P will qualify as a device deficiency. See Sections 6.1.2 and 8.5.
q. Dual energy X-ray absorptiometry and lateral X-ray imaging will be done during Screening to determine participant eligibility. Dual energy X-ray absorptiometry and X-ray imaging should be acquired and submitted for central independent review at least 10 days prior to Randomisation.
r. Dual energy X-ray absorptiometry must be performed before dosing at Week 26 and Week 52; however, it can be performed on the same day or in the days before dosing, but within the visit window.
s. A minimum of 8 hours fasting is required prior to blood collection, samples have to be collected in the morning between a window of 7:30 and 10:00 a.m. Participants should refrain from extensive physical exercise for 24 hours before blood collection.

Source: Module 5.3.5.1, Clinical protocol RGB-14-101 Amendment 2, Version 5.0, Table 1-1, page 16-18

Figure 12: Schedule of Assessments, Study RGB-14-101, Transition Period

Study Period	Days (weeks after first IMP administration)					
	Treatment Period 3					
Day(s)[a] (Week)	1 (52)[b]	8 (53)	15 (54)	30 (56)	90 (64)	183 (78) EOS/ ET
Window Period (Days)	± 4	± 1	± 1	± 1	± 3	± 4
General Assessments						
Inclusion/Exclusion Criteria Assessment for the Transition Period	X[c]					
Weight, Height, BMI[d]	X[c]					X
Re-randomisation	X[c]					
IMP Administration	X					
Pre-visit Phone Call[e]	X	X	X	X	X	X
Participant Identification and Visit Reminder Card[f]	X	X	X	X	X	X
Safety Assessments						
Physical Examination[g]	X[c]					X
Haematology and Clinical Chemistry	X[c, h]	X	X[i]	X	X	X
Urinalysis[j]	X[c]					X
12-lead ECG	X[c]					X
Vital Signs[k]	X[c]	X	X	X	X	X
Local Tolerance (Skin Examination)	X[l]	X				
Prior and Concomitant Medication[m]	◄					►
Adverse Events	◄					►
Medical Device Events[n]	X					
Efficacy Assessment						
DXA Scan Assessment	X[o]					X
Lateral Spine X-ray	X					X
Immunogenicity Assessment/Serum Drug Concentration Assessment						
Immunogenicity (binding ADAs and NAbs) Sampling	X[c]		X	X		X
Serum Drug Concentration Sampling	X[c]		X	X		X
PD						
PD (Serum CTX) Sampling[p]	X[c]					X
PD (Serum P1NP) Sampling[p]	X[c]					X

ADA = anti-drug antibody; BMI = body mass index; CTX = collagen C-telopeptide; DXA = dual energy x-ray absorptiometry; ECG = electrocardiogram; EOS = End-of-Study, ET = early termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IMP = investigational medicinal product; NAbs = neutralising antibodies; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic(s)

a. Day(s) refer to days within Screening or Treatment Period.
b. On Day 1 of Treatment Period 3 (Week 52) participants continuing to the Transition Period who received Prolia® during the Main Period will be re-randomised 1:1 to receive either a dose RGB-14-P or Prolia® in a double-blinded manner. Participants continuing to the Transition Period who received RGB-14-P during the Main Period will continue to receive a dose of RGB-14-P but will also follow the randomisation procedure to maintain blinding.
c. Procedure(s)/assessment/blood collection to be performed predose.
d. Height will be measured without shoes at all timepoints when BMI is measured.
e. All participants will be contacted by phone 1 day prior to every visit for assessing coronavirus disease 2019 symptoms and signs and if they had any contact with a person who has tested positive for severe acute respiratory syndrome coronavirus 2. During the pre-visit call participants will be reminded of fasting conditions for blood analysis (as applicable).
f. At each visit participants will be provided with a participant identification and visit reminder card. The Investigator must update the visit reminder card at each visit with the details for the next visit.
g. A comprehensive physical examination will include an assessment of general appearance and a review of systems (head, eyes, ears, nose, mouth/oral cavity, throat/neck, thyroid, lymph nodes, dermatologic, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal and neurologic systems).
h. Additional local calcium testing predose may be performed according to local practice or at Investigator's discretion.
i. Albumin-adjusted serum calcium only.
j. Sites will perform a urine dipstick. In case of abnormal results, a urine sample may be sent to the central laboratory for full analysis if deemed necessary by the Investigator. See Appendix 2 (Section 10.2).
k. Vital signs include measurement of blood pressure, pulse and body temperature. Respiratory rate to be assessed at the discretion of the Investigator. Systolic and diastolic blood pressure and pulse measurements will be assessed after the participant has been sitting for at least 5 minutes with back supported and both feet on the floor.
l. Injection site reaction assessment should be done predose and approximately 1 hour postdose, during this 1 hour period (i.e., from dosing to the injection site assessment) the participant will stay in the clinic for general safety observation. Any further assessment of the injection site or prolonged observation of the participant may be done at the discretion of the Investigator.
m. Compliance with daily calcium and vitamin D intake will be monitored and assessed throughout the study.
n. Information on medical device events (e.g., needle broken, dose not administered properly, syringe condition problem) and medical device events (device incident/deficiency) that caused adverse events or events that led to serious adverse events are to be reported by unblinded site staff in the Product Complaint Form and electronic case report form (adverse events and serious adverse events only) as described in the Addendum to Investigator Manual and the Product Complaint Procedure. A medical device event related to Prolia® will qualify as a device incident and a medical device event related to RGB-14-P will qualify as a device deficiency. See Sections 6.1.2 and 8.5.
o. Dual energy X-ray absorptiometry must be performed before dosing at Week 52; however, it can be performed on the same day or in the days before dosing, but within the visit window.
p. A minimum of 8 hours fasting is required prior to blood collection, samples have to be collected in the morning between a window of 7:30 and 10:00 a.m. Participants should refrain from extensive physical exercise for 24 hours before blood collection.

Source: Module 5.3.5.1, Clinical protocol RGB-14-101 Amendment 2, Version 5.0, Table 1-1, page 19-20

14.3.2. Eligibility Criteria, Study RGB-14-101

Key Inclusion Criteria

1. Postmenopausal women (defined as 12 months of spontaneous amenorrhea without an alternative medical cause with serum follicle-stimulating hormone levels falling in the normal postmenopausal range at the central laboratory at the time of the Screening Period, or females who underwent bilateral oophorectomy at least 6 weeks prior to the Screening Period).
2. Aged 60 to 80 years (inclusive) at the time of signing the informed consent.
3. Body weight ≥ 50 and ≤ 90 kg at Screening.
4. Absolute BMD consistent with T-score ≥ -4.0 and ≤ -2.5 at the lumbar spine, confirmed by central independent review at Screening.
5. At least two lumbar vertebrae (from L1 to L4) evaluable by DXA.
6. Naïve to denosumab, denosumab biosimilars, or romosozumab at Screening.
7. Had to have been enrolled, received both doses of the investigational product (IP), adequately complied with the protocol and completed the scheduled Main Period to enroll in the Transition Period.

Key Exclusion Criteria

1. History and/or presence of a severe or more than two moderate vertebral fractures as determined by central reading of lateral spine X-ray during Screening.
2. History and/or presence of hip fracture or bilateral hip replacement.
3. Presence of an active healing fracture.
4. Uncorrected Vitamin D deficiency (defined as serum 25-OH vitamin D level < 20 ng/mL [50 nmol/L]) at Screening.
5. Hyper- or hypocalcemia (defined as albumin-adjusted serum calcium for hypocalcemia < 2.1 mmol/L [8.4 mg/dL] or for hypercalcemia > 2.62 mmol/L [10.6 mg/dL]) at Screening.
6. Clinically significant leukopenia, neutropenia, or anemia as judged by the investigator.
7. Inadequate renal or hepatic function a Screening:
    a. Estimated glomerular filtration rate (eGFR) < 30 mL/min or on dialysis
    b. Serum alanine transaminase and aspartate transaminase ≥ 2 x upper limit of normal or total bilirubin ≥ 1.5 x upper limit of normal (except in Gilbert's syndrome, where the total bilirubin ≤ 2.5 upper limit of normal is accepted)
8. Known hypersensitivity (including severe allergic reactions) to monoclonal antibodies or a history of systemic hypersensitivity to any components of the IP, including latex allergy.
9. Known intolerance or malabsorption of calcium or vitamin D supplements.
10. Use of any of the following medications that can affect BMD:
    a. Oral bisphosphonate for osteoporosis treatment:
        i. Cumulative use for > 3 years at Screening.
        ii. Any use within 1 year prior to Screening.
    b. Intravenous bisphosphonate within 5 years prior to Screening.

c. Parathyroid hormone (PTH) or PTH analogues at any dose within 1 year prior to Screening.
d. Oral or topical (e.g., transdermal, intravaginal) estrogen, selective estrogen receptor modulators (SERMs), tibolone, or aromatase inhibitors within 1 year prior to Screening.
e. Calcitonin or its derivatives, calcimimetics (such as cinacalcet or etelcalcetide) within 6 months prior to Screening.
f. Systemic glucocorticoids (≥ 5 mg prednisone equivalence per day for ≥10 days or cumulative dose ≥ 50 mg) within 3 months prior to Screening.
    i. Topical and inhaled glucocorticoids are allowed.
g. Fluoride or strontium intended for osteoporosis treatment at any dose at any time.
h. Any IP not specified in the protocol for treatment of osteoporosis at any dose at any time.
i. Other bone active drugs at any dose within 3 months prior to Screening.

11. Non-osteoporosis medical conditions that could affect BMD at Screening.
    a. History of (within 5 years prior to Screening) and/or current, hyper- or hypoparathyroidism, other than clinically insignificant secondary hyperparathyroidism.
    b. Current uncontrolled hyper- or hypothyroidism.
    c. History of bone disease such as osteomalacia, osteogenesis imperfecta, osteopetrosis, achondroplasia, or Paget's disease of the bone.
    d. History of metabolic or other endocrinologic diseases such as malabsorption syndrome, Cushing disease, acromegaly, or hyperprolactinemia.
12. History of osteonecrosis of the jaw (ONJ) or risk factors for ONJ (e.g., heavy smoking, poor oral hygiene, invasive dental procedures without complete healing or planned during the study), osteonecrosis of the external auditory canal, or atypical femoral fracture at Screening.
13. Active infection, or positive testing for hepatitis B or C or human immunodeficiency virus at Screening.
14. History of significant cardiac disease of or electrocardiogram (ECG) abnormalities indicating safety risk at Screening.
15. Malignancy within 5 years prior to Screening.
    a. Completely excised and cured non-metastatic squamous or basal cell carcinoma of the skin or cervical carcinoma in situ was permitted.
16. Current or past alcohol or drug abuse.
17. Any other clinically significant disorder/disease/condition or laboratory abnormality which, in the opinion of the Investigator, would post a risk to participant safety or interfere with the study evaluation, procedures, or completion.

14.4. Statistical Appendices

Secondary Endpoints

There were no key efficacy confirmatory secondary endpoints prespecified in this study. There were no multiplicity adjustments made for the secondary endpoints. These endpoints are used as exploratory endpoints to support the primary endpoint. The results shown in Tables 41-43 are conducted on the FAS population.

Table 40 shows the difference in means in the percent change from baseline for total hip BMD at weeks 26 and 52. The results have a similar trend as the primary endpoint results.

Table 40. Secondary Endpoint: Percent Change in Baseline in Total Hip BMD at Weeks 26 and 52 – Period 1 Full Analysis Set

	RGB-14-P N=242	**Prolia N=231**
Baseline mean total hip (SD)	0.77 (0.09)	0.77 (0.10)
Week 26		
n	225	211
LS means (g/cm^2) (95% CI)	1.15 (0.38, 1.92)	1.46 (0.70, 2.22)
Treatment difference (RGB-14-P -Prolia)	-0.31	
95% CI	-0.79, 0.17	
Week 52		
n	220	205
LS means (g/cm2) (95% CI)	2.16 (1.38, 2.94)	2.32 (1.55, 3.10)
Treatment difference (RGB-14-P -Prolia)	-0.16	
95% CI	-0.68, 0.36	

Source: Clinical Study Report (18-Month CSR) Table 11-7, page 139
Abbreviations: BMD, bone mineral density; N, total number of participants; n, total number of participants at that timepoint; SD, standard deviation

Table 41 shows the difference in means in the percent change from baseline for lumbar spine BMD at week 26. The results have a similar trend as the primary endpoint results.

Table 41. Secondary Endpoint: Percent Change in Baseline in Lumbar Spine BMD by DXA at Week 26 – Period 1 Full Analysis Set

	RGB-14-P N=242	Prolia N=231
Baseline mean lumbar spine (SD)	0.77 (0.06)	0.78 (0.07)
n	227	218
LS Means (95% CI)	2.51 (1.34, 3.67)	2.47 (1.33, 3.62)
Treatment difference (RGB-14-P -Prolia)	0.03	
95% CI[2]	-0.70, 0.77	

Source: Clinical Study Report (18-Month CSR) Table 11-11, page 146
Abbreviations: BMD, bone mineral density; N, total number of participants; n, total number of participants at that timepoint; SD, standard deviation

Table 42 shows the difference in means in the percent change from baseline for femoral neck BMD at weeks 26 and 52. The results have a similar trend as the primary endpoint results.

Table 42. Secondary Endpoint: Percent Change in Baseline in Femoral Neck BMD at Weeks 26 and 52 – Period 1 Full Analysis Set

	RGB-14-P N=242	Prolia N=231
Baseline mean total hip (SD)	0.71 (0.10)	0.71 (0.11)
Week 26		
n	225	211
LS means (g/cm^2) (95% CI)	0.75 (-0.31, 1.80)	0.87 (-0.18, 1.92)
Treatment difference RGB-14-P -Prolia	-0.12	
95% CI	-0.73, 0.48	
Week 52		
n	237	235
LS means (g/cm2) (95% CI)	1.26 (0.18, 2.34)	1.58 (0.51, 2.66)
Treatment difference RGB-14-P -Prolia	-0.32	
95% CI	-1.01, 0.36	

Source Clinical Study Report (18-Month CSR) Table 11-17, page 154
Abbreviations: BMD, bone mineral density; N, total number of participants; n, total number of participants at that timepoint; SD, standard deviation

Subgroups

Upon request from FDA, the Applicant conducted subgroup analysis by region (USA vs Outside of USA), ethnicity, age, and race (white, black, Asian, etc.). Due to a very small number of participants in race other than White, the estimates for the 90% CIs were not able to be calculated for race. Table 43 shows the demographic information for race. The Applicant gave descriptive data for region (USA vs Outside of USA), ethnicity (Hispanic or Latino vs. Not Hispanic or Latino), and statistical subgroup analysis by age (age < 65 years vs age ≥ 65 years) (Table 44). Table 45 shows the subgroup analysis of the difference in means up to Week 52. The subgroup analyses were performed using the Applicant FAS defined population.

Table 43. Subject Demographics - Main Period (Full Analysis Set for Main Period), RGB 14-101 CSR

Characteristic	Statistic	RGB-14-P (N = 242)	Prolia (N = 231)	Overall Study (N = 473)
Age (years)	n	242	231	473
	Mean	66.7	66.8	66.7
	SD	5.20	4.91	5.06
	Median	66.0	66.0	66.0
	Minimum	60	60	60
	Maximum	83	84	84
Ethnic Origin				
Hispanic or Latino	n (%)	18 (7.4)	22 (9.5)	40 (8.5)
Not Hispanic or Latino	n (%)	223 (92.1)	209 (90.5)	432 (91.3)
Not Reported	n (%)	1 (0.4)	0	1 (0.2)
Race				
White	n (%)	241 (99.6)	229 (99.1)	470 (99.4)
Black or African American	n (%)	0	2 (0.9)	2 (0.4)
Native Hawaiian or Other Pacific Islander	n (%)	1 (0.4)	0	1 (0.2)
Country				
United States of America	n (%)	11 (4.5)	9 (3.9)	20 (4.2)
Spain	n (%)	13 (5.4)	22 (9.5)	35 (7.4)
Bulgaria	n (%)	40 (16.5)	27 (11.7)	67 (14.2)
Hungary	n (%)	19 (7.9)	20 (8.7)	39 (8.2)
Ukraine	n (%)	1 (0.4)	2 (0.9)	3 (0.6)
Italy	n (%)	8 (3.3)	15 (6.5)	23 (4.9)
Czechia	n (%)	25 (10.3)	36 (15.6)	61 (12.9)
Poland	n (%)	125 (51.7)	100 (43.3)	225 (47.6)

N = The number of subjects in the analysis set; n = The number of subjects in the specific category; SD = standard deviation.

*%: calculated using the number of subjects in the analysis set as the denominator (n/N*100).*

Source: RESPONSE to FDA Clinical Information Request, December 10, 2024, BLA 761439 Table 2, page11

Table 44. Summary of Percent Chane from Baseline in Lumbar Spine Bone Mineral Density (g/cm2) Results by Visit - Main Period (Full Analysis Set for Main Period)

Subgroup	RGB-14-P N=242	Prolia N=231	Overall Study N=473
Ethnicity			
Hispanic or Latino, mean (SD)	5.65 (2.96)	5.62 (3.55)	5.63 (3.26)
Not Hispanic or Latino, mean (SD)	5.60 (3.55)	5.15 (4.17)	5.39 (3.86)
Region			
USA, mean (SD)	6.03 (2.29)	4.59 (3.15)	5.35 (2.74)
Non-USA, mean (SD)	5.59 (3.55)	5.22 (4.15)	5.41 (3.85)

Source: RESPONSE to FDA Clinical Information Request, December 10, 2024, BLA 761439 Table 4, page 14-15; Table 5, page 15-16; Table 46, page 84-85, Table 47, page 85-86
Abbreviations: SD: standard deviation

Table 45. Analysis of Percent Chane from Baseline Lumbar Spine Bone Mineral Density (g/cm2) at Week 52 - Subgroup: Age - Full Analysis Set for Main Period

	RGB-14-P N=100	Prolia N=86
Non superiority test		
Age < 65		
LS Means	4.58	4.37
Treatment difference (RGB-14-P -Prolia)	0.21	
95% CI[2]	-0.79, 1.21	
Age ≥ 65		
LS Means	5.67	4.98
Treatment difference (RGB-14-P -Prolia)	0.70	
95% CI[2]	-0.13, 1.52	
Non inferiority test		
Age < 65		
LS Means	5.71	5.74
Treatment difference (RGB-14-P -Prolia)	-0.03	
95% CI[2]	-1.03, 0.98	
Age ≥ 65		
LS Means	4.99	4.70
Treatment difference (RGB-14-P -Prolia)	0.29	
95% CI[2]	-0.54, 1.11	

Source: RESPONSE to FDA Clinical Information Request, December 10, 2024, BLA 761439 Table 68, page 116; Table 69, page 116; Table 70, page 117; Table 71, page 117

The analysis is performed with an ANCOVA model with %CfB in lumbar spine BMD at Week 52 as the dependent variable; covariates are treatment Arm (RGB-14-P and US-licensed Prolia), stratification factors at randomization (Previous use of bisphosphonates [yes/no] and geographical region [Europe, US], Baseline BMD value in lumbar spine, machine type and machine type*baseline BMD value interaction. Estimated difference: RGB-14-P - Prolia.)
Bone Mineral Density (BMD) analysed in this table is corrected for instrument quality control (IQC) and cross
Missing values are imputed under the corresponding null hypothesis of non-superiority or non-inferiority.
Abbreviations: CI: Confidence Interval

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