BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	BLA 351(k)
Application Number	761444
Received Date	August 30, 2024
BsUFA Goal Date	August 30, 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	HLX14
Proposed Nonproprietary Name[1]	denosumab-nxxp
Proposed Proprietary Name[1]	Bildyos (proposed interchangeable biosimilar to US-Prolia) Bilprevda (proposed interchangeable biosimilar to US-Xgeva)
Pharmacologic Class	RANK Ligand (RANKL) inhibitor
Applicant	Shanghai Henlius Biotech, Inc.
Applicant Proposed Indication(s)	Bildyos (proposed interchangeable biosimilar to US-Prolia): • Treatment of postmenopausal women with osteoporosis at high risk for fracture. • Treatment to increase bone mass in men with osteoporosis at high risk for fracture. • Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture. • Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. • Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. Bilprevda (proposed interchangeable biosimilar to 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.

[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.

Biosimilar Multidisciplinary Evaluation and Review (BMER) 351(K) BLA, BLA 761444, HLX14, a proposed interchangeable biosimilar to U.S.-licensed Prolia and U.S.-licensed Xgeva

Recommendation on Regulatory Action	Approval for HLX14 as a biosimilar to US-Prolia and US-Xgeva Provisional determination that HLX14 meets the applicable standards of interchangeability with US-Prolia and US-Xgeva. Approval of interchangeability is precluded due to unexpired first interchangeable exclusivity for Jubbonti and Wyost.

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OPQAIII = Offices 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
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health

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
IP	Investigational Product
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 (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-Prolia are different from the indications and strength of US-Xgeva.

The Applicant proposes HLX14 as an interchangeable biosimilar product to US-Prolia and US-Xgeva and the proposed proprietary names are Bildyos and Bilprevda, respectively.

The Applicant seeks the same indications for HLX14 as those which are approved for US-Prolia and US-Xgeva. The strengths, dosage form, route of administration, indications, and dosing regimens for HLX14 will be the same as those of US-Prolia and US-Xgeva. They are listed below:

Bildyos:
Strength: 60 mg/1 mL
Dosage form: injection
Route of administration: subcutaneous (SC)
Dosing regimen: 60 mg injected SC every six months
Indications:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as 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 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

Bilprevda
Strength: 120 mg/1.7 mL
Dosage form: injection
Route of administration: subcutaneous (SC)
Dosing regimen: 120 mg injected SC every four weeks
Indications:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors (120 mg injected 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 receptor activator of the nuclear factor kappa-B ligand (RANKL), 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 HLX14 has the same mechanism(s) of action as those of US-Prolia and US-Xgeva. The Applicant performed a comparative analytical assessment of HLX14, US-Prolia, US-Xgeva. The data provided support the conclusion that HLX14 is highly similar to US-Prolia and US-Xgeva. HLX14 has the same route of administration, dosage form, strengths, and conditions of use as those of US-Prolia and of US-Xgeva. Refer to Section 1.1 for details.

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.

HLX14 is proposed as below:

For subcutaneous injection:

- Single-dose prefilled syringe containing 60 mg in 1 mL solution.
- Single-dose vial containing 60 mg in 1 mL solution.
- Single-dose vial containing 120 mg in 1.7 mL (70 mg/mL) solution.

1.4. Inspection of Manufacturing Facilities

Pre-license on-site inspections (PLI) were conducted at Shanghai Henlius Biologics Co., Ltd., (b) (4) Shanghai, China (FEI: 3023420030), listed in this application as the HLX14 drug substance (DS) manufacturing facility, as well as at Shanghai Henlius Biologics Co., Ltd., (b) (4) Shanghai, China (FEI 3023420030), listed as the HLX14 drug product (vial and PFS presentations) manufacturing facility. At the conclusion of the inspections, FDA conveyed deficiencies to the respective representatives of the facilities along with the initial "VAI" classification for (b) (4) and "OAI/withhold" for (b) (4) by the Agency. Henlius responded and provided adequate response and descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy to address the deficiencies communicated in Form FDA 483. The initial "withhold" classification was revised and approval was recommended for the DS and DP manufacturing facilities. Overall, all proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

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

Shanghai Henlius provided adequate data to establish the scientific bridge to justify the relevance of data generated from the study 002-PMOP301, which used EU-PROLIA as the non-U.S.-licensed comparator product, to the assessment of biosimilarity:

- The Office of Pharmaceutical Products (OPQ), CDER has determined, and I agree, that based on the data provided by the Applicant, the analytical data provided establish the analytical component of the scientific bridge.
- The Office of Clinical Pharmacology (OCP) has determined, and I agree, that based on the data provided by the Applicant, the pharmacokinetic (PK) data establish a PK component of the scientific bridge.[2]

[2] It should be noted that there is a pending citizen petition that requests certain revisions to FDA's guidance recommendations regarding the use of non-U.S.-approved comparators in development programs intended to demonstrate biosimilarity to, or interchangeability with, the U.S.-licensed reference product (see Docket No. FDA-2025-P-1098 at www.regulations.gov). The issues raised by this citizen petition are under review by FDA. This review is consistent with FDA's current guidance recommendations and does not represent a final decision by FDA on the issues raised in the pending citizen petition. When FDA issues a response to the citizen petition, it will be publicly available at www.regulations.gov.

1.6. Biosimilarity and Interchangeability Assessment

Comparative Analytical Studies[3]	
Summary of Evidence	• The comparative analytical assessment included comparisons between HLX-14 and US-Prolia and HLX14 and US-Xgeva. • HLX14 is highly similar to US-Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components. HLX14 has the same strengths, dosage form, and route of administration as US-Prolia and US-Xgeva.
Assessment of Residual Uncertainties	• There are no residual uncertainties form the product quality assessment.
Animal/Nonclinical Studies	
Summary of Evidence	• The information in the pharmacology/toxicology assessment supports the demonstration of biosimilarity
Assessment of Residual Uncertainties	• There are no residual uncertainties from the pharmacology/toxicology assessment
Clinical Studies	
Clinical Pharmacology Studies	
Summary of Evidence	• Pharmacokinetic (PK) similarity between HLX14 and US-Prolia was demonstrated in healthy male subjects in Study HLX14-001 and supports demonstration of no clinically meaningful differences between HLX14 and US-Prolia. • Because of demonstrated analytical similarity between HLX14 and US-Xgeva and US-Prolia, PK data from Study HLX14-001 also support the conclusion that HLX14 would be expected to have similar PK as US-Xgeva. Additionally, comparative PK data generated with the 60 mg/1 mL (US-Prolia) strength are relevant for conclusions about PK similarity for the 120 mg/1.7 mL (US-Xgeva) strength. • PK similarity between EU-Prolia and US-Prolia in Study HLX14-001 provides a PK component of the

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

	scientific bridge to support the relevance of comparative data generated using EU-Prolia to the assessment of biosimilarity in Study HLX14-002-PMOP30. • Comparable denosumab exposure between HLX14 and EU-Prolia was observed in postmenopausal women with osteoporosis supporting the conclusion that HLX14 would be expected to have similar PK as US-Prolia. (Study HLX14-002-PMOP30) • Immunogenicity data from Studies HLX14-001 (healthy male subjects) and HLX14-002-PMOP301 (female subjects with postmenopausal osteoporosis) support the demonstration that HLX14 has no clinically meaningful differences from US-Prolia because the incidence of ADAs and NAbs was similar between the treatment arms for each study. • There was no apparent impact of ADA and NAb on study drugs' PK, PD, safety, and efficacy. • Therefore, the data support that HLX14 has no clinically meaningful differences from US-Prolia and US-Xgeva.
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 HLX14-002-PMOP301) in 514 post-menopausal women with osteoporosis to compare the PK, pharmacodynamics (PD), efficacy, safety, and immunogenicity of HLX14 and EU-Prolia. Subjects were randomized to receive HLX14 or EU-Prolia 60 mg injected SC every six months for one year (Core Treatment Period). After one year, subjects initially assigned to EU-Prolia in the Core Treatment Period were re-randomized to either continue EU-Prolia or transition to HLX14. Subjects who received HLX14 during the Core Treatment Period continued their treatment with HLX14. Subjects were followed for six months after the third dose of study drug. • This study demonstrated that HLX14 and EU- 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 HLX14 and EU-Prolia were comparable. The adverse events observed were consistent with the known safety profile of denosumab (as labeled in the U.S.-Prolia USPI). There were no meaningful differences in the incidence of specific adverse events between HLX14 and U.S.-Prolia, and the small differences in incidences of some of the treatment emergent adverse events (TEAE) that were observed in the HLX14 and EU-Prolia arms was likely due to chance. The adverse event profile of subjects transitioning from U.S.-Prolia to HLX14 was comparable to the adverse event profile of subjects that continued on U.S.-Prolia These differences were also likely due to chance, and likely do not represent a meaningful difference in safety. • The study also demonstrated similarity of HLX14 and EU-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 HLX14. • 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 HLX14 and US-Prolia or HLX14 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 HLX14 can be

	expected to produce the same clinical result as that of US-Prolia and US-Xgeva 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 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 HLX14 as an interchangeable biosimilar to US-Prolia and US-Xgeva for the following indications for which US-Prolia and US-Xgeva have been previously approved: o Treatment of post-menopausal women with osteoporosis at high risk for fracture. o Treatment to increase bone mass in men with osteoporosis at high risk for fracture. o Treatment of glucocorticoid-induced osteoporosis in men and women who are at high risk for fracture. o Treatment to increase bone mass in men at high for fracture receiving androgen deprivation therapy for prostate cancer. o Treatment to increase bone mass in women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. o Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors o 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 HLX14 as an interchangeable biosimilar 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 HLX14 is highly similar to US-Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between HLX14 and US-Prolia, or between HLX14 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 HLX14 can be expected to produce the same clinical result as US-licensed Prolia and US-licensed Xgeva in any given patient. The risk in terms of safety or diminished efficacy of alternating or switching between use of HLX14 and US-Prolia or between HLX14 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 HLX14 can be expected to produce the same clinical result as U.S.-Prolia and U.S.-Xgeva in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between use of the HLX14 and U.S.-Prolia, or HLX14 and U.S.-Xgeva, is not greater than the risk of using U.S.-Prolia or U.S.-Xgeva without alternation or switch. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that HLX14 is biosimilar to US-Prolia and US-Xgeva and meets the statutory criteria to be interchangeable with U.S.-Prolia and U.S.-Xgeva as follows:

- HLX14, 60 mg/mL injection for SC use in a single-dose vial and in a single-dose PFS as interchangeable biosimilars to US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS,
- HLX14, 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 HLX14:

US-Prolia:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as 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 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 (120 mg injected 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).

Healthcare providers have administered US-Prolia to all patient populations. The HLX14 vial may be licensed as interchangeable with US-Prolia PFS given that the difference between a vial and a PFS would not be expected to result in any clinically meaningful difference in this case, as healthcare providers can be expected to manage risks associated with administering to patients using a vial or a PFS in accordance with the administration instructions in the labeling.

FDA has not identified any deficiencies that would justify a complete response action and has provisionally determined that HLX14 meets 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 HLX14 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 761444 will be administratively split to facilitate an approval action for HLX14 as biosimilar to US-Prolia and US-Xgeva ("Original 1") and a provisional determination that HLX14 would be interchangeable with US-Prolia and US-Xgeva ("Original 2"), but for unexpired exclusivity.

The review team recommends approval of HLX14 as a biosimilar product as follow:

- HLX14, 60 mg/mL injection for SC use in a single-dose vial and in a single-dose PFS are biosimilar to US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS, and
- HLX14, 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:

- HLX14, 60 mg/mL injection for SC use in a single-dose vial and in a single-dose PFS meet the applicable standards for interchangeability with US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS, and
- HLX14, 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 761444/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 761444 Original 2 will become eligible for approval.

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

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2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

The Division of General Endocrinology and Division of Oncology I and II had communication meetings with the Applicant during the development of HLX14. The corresponding IND for BLA 761444 is PIND 153872. The summary of regulatory history is provided in Table 1 below.

Table 1: Summary of Regulatory History

February 23, 2021 (BPD 2)	To support a 351 (k) application, the Applicant proposed to conduct a two-part PK study that includes HLX14, US-Prolia, EU-Prolia, and China sourced Prolia, and comparative clinical study in post- menopausal women to compare HLX14 and EU-approved Prolia. A comparative analytical assessment that directly compares HLX14 to US-Prolia, and EU-Prolia and should meet the pre-specified acceptance criteria for analytical and PK similarity to establish a scientific bridge.
February 23, 2023 (BPD 2b)	FDA agreed with Henlius's proposal to develop HLX14 vial and PFS for US-Prolia, in which US-Prolia has only PFS presentation. Henlius will need to compare the proposed HLX14 PFS with US-Prolia PFS. Henlius asked if a HF informative analysis and HF validation study for HLX14 PFS are not required based on the URRA and threshold analysis. To support biosimilarity, the Agency advised the Sponsor to include URRA to HLX14 and a comparative analysis comparing HLX14 to a model of the same or similar device that is approved in the US.
May 17, 2024 (BPD 2a)	The Agency provided additional information needed regarding the sponsor's proposed (b) (4) control of susceptible contamination and guidance on use of PFS (b) (4) The Agency expressed concerns (b) (4)

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 HLX14.

The clinical studies are described in Table 2.

Table 2: Relevant Submitted Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study					
Study HLX14-001	n/a	PK (Part 2): Compare the pharmacokinetics, pharmacodynamics, safety and immunogenicity of HLX14, US-Prolia, EU-Prolia, and China-(CN) Prolia	Double-blind, randomized, parallel-group, active-controlled, three-way pairwise	Healthy Subjects	Pilot PK (part 1) n=24 1:1 ratio comparing HLX14 and EU-Prolia single dose 60 mg SC PK similarity study (part 2)- n=228, 1:1:1:1 comparing HLX14 vs US-Prolia vs EU-Prolia vs CN-Prolia single dose 60 mg SC
Comparative Clinical Study(ies)					
Study 002-PMOP301	n/a	Compare the PK, PD, safety and immunogenicity of HLX14 vs EU-Prolia	Double-blind, randomized, parallel-group, active-controlled	Post menopausal women with osteoporosis	**Main Period (baseline to week 52)** HLX14 60 mg vial SC q6 mo (256) **Extension Period (week 52-78)** EU-Prolia 60 mg PFS SC q 6 mo (258) 220 from EU-Prolia will be randomized: 110 to EU-Prolia/ HLX14 and 110 EU-Prolia 220 subjects in HLX14 will continue into HLX14

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3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761444 for HLX14 manufactured by Henlius Biologics Co., Ltd. The data submitted in this application are adequate to support the conclusion that the manufacture of HLX14 is well-controlled and leads to products that are safe, pure, and potent. The comparative analytical data support the demonstration that HLX14 is highly similar to US-licensed Prolia and US-licensed Xgeva, notwithstanding minor differences in clinically inactive components. The analytical component of the scientific bridge was established to support the use of EU-approved Prolia (EU-Prolia) as a comparator in clinical studies supporting this application. OPQAIII is recommending that this product be approved for human use under conditions specified in the package insert.

3.2. Devices

Bildyos is supplied as a drug-device combination product, and each prefilled syringe contains 60 mg of HLX14, as well as in a single-dose vial presentation that is not considered a drug-device combination product. Bilprevda is supplied as a single-dose vial, and hence, is not considered a drug-device combination product.

3.2.1. Center for Devices and Radiological Health (CDRH)

CDRH was consulted for the review of the device constituent part of the Bildyos drug-device combination product.

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

The CDRH review team has concluded that the device constituent parts of the combination products are acceptable. Refer to the CDRH consult review dated April 21, 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 analysis (CA), to determine if Human Factors (HF) Validation study and Comparative Use Human Factors (CUHF) study are required to support the marketing application for Bildyos as an interchangeable biosimilar to U.S.-Prolia.

The DMEPA-1 review team concluded that the Applicant does not need to submit HF Validation and CUHF studies results for Bildyos PFS as part of this application, and the proposed product can be approved.

Refer to the DMEPA-1 review dated March 11, 2024, under IND 153782 in DARRTS for the review of the URRA and comparative analyses and additional details.

Refer to the DMEPA-1 review dated March 22, 2024, under BLA 761444 in DARRTS for the DMEPA's assessment that CUHF results are not needed and additional details.

3.3. Office of Study Integrity and Surveillance (OSIS)

An OSIS audit request was requested for Study HLX14-001. The study was conducted at three clinical sites and used one analytical site:

- Clinical site 1: Huashan Hospital, Shanghai, China
- Clinical site 2: Shuguang Hospital, Shanghai, China
- Clinical site 3: Wuxi People's Hospital, Wuxi, China
- Analytical site: Shanghai Jollin Lab Co., Ltd., Shanghai, China

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed for Clinical site 1 (Huashan Hospital, Shanghai, China) and Clinical site 2 (Shuguang Hospital, Shanghai, China). The rationale for this decision is that although OSIS has no prior inspection history for these sites, inspections are not needed because OSIS had an inspection for the other clinical site (Clinical site 3, Wuxi People's Hospital, Wuxi, China) listed on the consult which enrolled the majority of subjects for the study, and which will provide some assurance of the overall conduct of the study. (refer to OSIS review dated June 26, 2025, in DARRTS). The inspection for the analytical site at Shanghai Jollin Lab Co., Ltd., Shanghai, China, has been completed and no objectionable conditions were observed (refer to OSIS review dated June 27, 2025, in DARRTS).

The inspection for the clinical site at Wuxi People's Hospital, Wuxi, China has been completed. Objectionable conditions were found during the inspection and Form FDA 483 was issued at the inspection close-out. There was also one discussion item addressed at the close of the inspection. After reviewing the inspectional findings, the exhibits provided in EIR, and the clinical investigator's response to Form FDA 483 and the discussion item, OSIS had concerns regarding the safeguarding the rights and welfare of human subjects, specifically with respect to the site's provision of false information during the medical counseling of a subject and his partner, which appears to have resulted in termination of a pregnancy conceived during the subject's participation of the study. OSIS also concluded there were two regulatory violations under 21 CFR 312. However, the observations and discussion item do not impact the reliability of the data for inspected study HLX14-001. (refer to OSIS review dated July 10, 2025, in DARRTS).

3.4. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted an inspection on Site # 11115 in Tianjing, China from February 17-20, 2025, Site #11130 in Hunan, China from February 24-28, 2025, Site CRO in Shanghai, China from February 24-27, 2025. OSI concluded that based on the overall inspection results of these clinical investigators (CIs) and the Sponsor, and the regulatory assessments, the data generated by the CIs and submitted by the Sponsor are verifiable. Study HLX14-002-PMOP301 appears to have been conducted adequately and the clinical data submitted by the Sponsor appear acceptable in support of the respective indication. Refer to OSI reviewed dated May 16, 2025, in DARRTS for additional details.

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4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

Shanghai Henlius Biotech, Inc (Henlius) developed HLX14 (denosumab-nxxp) to be an interchangeable biosimilar to US- Prolia and US-Xgeva. Denosumab is a monoclonal antibody to RANK ligand (RANKL). The Applicant seeks licensure for HLX14 and proposes the same strengths, dosage form, route of administration, indications, and dosing regimen as US-Prolia and US-Xgeva. The HLX14 product is presented in a 60 mg/mL single use pre-filled syringe (PFS) and vial for administration of 60 mg denosumab every 6-months, while the HLX14 interchangeable biosimilar to US-Xgeva is presented as a single dose 120 mg/1.7 mL (120 mg) vial for subcutaneous administration every 4-weeks.

Animal studies were not conducted in support of the application, and none were considered necessary as agreed during BPD type 2 and type 4 pre-submission meetings. The nonclinical toxicity of denosumab is related to its affinity to RANKL and related biological activity. Thus, in vitro physicochemical, and functional characterizations of denosumab products are considered sufficient and more sensitive than animal studies to detect any functional differences (e.g., in affinity to RANKL and receptor activity) between HLX14 and reference products. The Applicant has conducted in vitro functional evaluations, testing for immunochemical properties (FcγR, FcRn and C1q binding) and in vitro biological activity (RANKL binding, neutralization activity, inhibition of osteoclast differentiation, ADCC-NK, and CDC) and other testing as part of the Comparative Analytical Assessment. The physicochemical characterization and functional activity studies support that HLX14, US-Prolia, and US-Xgeva are highly similar. See full review by Office of Product Quality Assessment 3 (OPQA3).

In conclusion, no animal studies with HLX14 and US-Prolia or US-Xgeva were needed to support this 351(k) application and the results of the in vitro studies support a demonstration of biosimilarity.

4.1.1. Nonclinical Residual Uncertainties Assessment

There are no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The HLX14 product is presented in a 60 mg/mL single use PFS and vial for administration of 60 mg every 6-months as a biosimilar to US-Prolia and as a single dose 120 mg/1.7 mL vial for administration of 120 mg every 4-weeks as a biosimilar to US-Xgeva. Both the PFS and vial presentations are sterile solutions for subcutaneous injection and contain the same drug product components (Table 3).

Comments on Excipients

The excipients in HLX14 are qualitatively identical to the excipients in US-Prolia and US-Xgeva. Drug product formulations are shown in the Applicant's Table 3 and Table 4. The Applicant did not provide a tabular comparison of HLX14 excipients and those of US-Prolia and US-Xgeva. The review determined slight quantitative differences in excipients compared to US-Prolia and US-Xgeva, but the minor differences do not impact the product safety profile.

Table 3 – Drug Product Formulation (60 mg, Biosimilar to Prolia)

Composition of HLX14 (60mg, PFS) Solution for Injection

Component	Concentration (mg/mL)	Content (mg/PFS)[1]	Quality standard
Denosumab	60	60	In-house
Acetic acid, glacial	1.02	1.02	USP & Ph. Eur. <0590>
Sorbitol	47.0	47.0	USP & Ph. Eur. <0435>
Polysorbate 20	0.1	0.1	USP & Ph. Eur. <0426>
Water for Injections	q.s.[2]	q.s.[2]	USP & Ph. Eur. <0169>
Sodium hydroxide	q.s.[2, 3]	q.s.[2, 3]	USP & Ph. Eur. <0677>

[1]: calculate based on the label volume (1 mL).
[2]: q.s. means *quantum sufficit.*
[3]: adjust the pH to 5.2 with an appropriate amount sodium hydroxide.

Composition of HLX14 (60 mg, vial) Solution for Injection

Component	Concentration (mg/mL)	Content (mg/ vial)[1]	Quality standard
Denosumab	60	60	In-house
Acetic acid, glacial	1.02	1.02	USP & Ph. Eur. <0590>
Sorbitol	47.0	47.0	USP & Ph. Eur. <0435>
Polysorbate 20	0.1	0.1	USP & Ph. Eur. <0426>
Water for injection	q.s.[2]	q.s.[2]	USP & Ph. Eur. <0169>
Sodium hydroxide	q.s.[2, 3]	q.s.[2, 3]	USP & Ph. Eur. <0677>

[1]: calculate based on the label volume (1 mL).
[2]: q.s. means *quantum sufficit.*
[3]: adjust the pH to 5.2 with an appropriate amount of sodium hydroxide.

Table 4 – Drug Product Formulation (120 mg, Biosimilar to Xgeva)

Composition of HLX14 (120 mg, vial) Drug Product

Component	Concentration (mg/mL)	Content (mg/vial)[1]	Quality standard
Denosumab	70	120	In-house
Acetic acid, glacial	1.08	1.84	USP & Ph. Eur. <0590>
Sorbitol	46.0	78.2	USP & Ph. Eur. <0435>
Polysorbate 20	0.1	0.17	USP & Ph. Eur. <0426>
Water for injections	q.s.[2]	q.s.[2]	USP & Ph. Eur. <0169>
Sodium hydroxide	q.s.[2, 3]	q.s.[2, 3]	USP & Ph. Eur. <0677>

[1]: calculate based on the label volume (1.7 mL).
[2]: q.s. means *quantum sufficit.*
[3]: adjust the pH to 5.2 with an appropriate amount of sodium hydroxide.

Comments on Impurities of Concern

The Applicant has reported that the product- and process-related impurities are below predetermined acceptance limits. The levels of each of these impurities were consistently lower than specified the limits among the batches of drug substances

tested and there are no toxicological concerns.

No extractable or leachable compounds of concern were identified during the assessments of container closure systems. Overall, no impurities or degradants of toxicologic concern were identified.

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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	• PK similarity between HLX14 and US-Prolia was demonstrated in Chinese healthy male subjects (Study HLX14-001). • PK similarity between EU-Prolia and US-Prolia in Study HLX14-001 provides a PK component of the scientific bridge to support the relevance of comparative data generated using EU-Prolia to the assessment of biosimilarity in Study HLX14-002-PMOP30. • Comparable study drug exposure between HLX14 and EU-Prolia was observed in postmenopausal women with osteoporosis supporting the conclusion that HLX14 would be expected to have similar PK as US-Prolia. (Study HLX14-002-PMOP30) • PK data from Study HLX14-001 also support the conclusion that HLX14 would be expected to have similar PK as US-Xgeva because comparative PK data generated with the 60 mg/1 mL strength are relevant for conclusions about PK similarity for the 120 mg/1.7 mL strength. • The results support a demonstration that HLX14 has no clinically meaningful differences from US-Prolia and US-Xgeva.
Immunogenicity	• Immunogenicity data from Studies HLX14-001 (healthy male subjects) and HLX14-002-PMOP301 (female subjects with postmenopausal osteoporosis) support the demonstration that HLX14 has no clinically meaningful differences from US-Prolia and EU-Prolia because the incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) was similar between the treatment arms

	for each study. This conclusion is based on the very low and comparable incidence of ADAs and NAbs. observed across treatment arms in both studies. • There was no apparent impact of ADA and NAb on study drugs' PK, PD, safety and efficacy. Therefore, the immunogenicity data also support that HLX14 has no clinically meaningful differences from US-Prolia and US-Xgeva.

The clinical development program of HLX14 included two clinical studies:

1. Study HLX14-001 was a randomized, parallel, single-dose study of HLX14 versus US, EU and China (CN)-Prolia in Chinese healthy adult male subjects for comparison in pharmacokinetic characteristics, safety, and Immunogenicity.

   This study was conducted in 2 parts. Part I was an open-label, randomized, parallel-controlled, single-dose, pilot study conducted in healthy adult male subjects. Part II was a double-blinded, randomized, four-arm, parallel-controlled, single-dose, PK similarity study conducted in healthy adult male subjects. Total of 228 subjects were enrolled in Part 2 to demonstrate PK similarity and randomized in a 1:1:1:1 ratio to receive a single dose (60 mg) of HLX14, EU-approved Prolia, US-licensed Prolia, and China (CN)-approved Prolia (not relevant to US approval).

2. Study HLX14-002-PMOP301 was a randomized, double-blind, international multicenter, parallel-controlled comparative clinical study to evaluate HLX14 versus EU-Prolia in postmenopausal women with osteoporosis at high risk of fracture.

The Clinical Pharmacology review for this BLA primarily focused on the PK similarity study (Part II of HLX14-001) and additional PK and immunogenicity data from the comparative clinical study (HLX14-002-PMOP301).

PK similarity between HLX14, EU-Prolia, and US-Prolia was demonstrated given that the 90% confidence intervals (CIs) for the ratios (HLX14/EU-Prolia, HLX14/US-Prolia and EU-Prolia/US-Prolia) of geometric means for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max} were all contained within the pre-specified equivalence limits [0.80; 1.25] (Table 6).

The results also established a PK component of the scientific bridge that justifies the relevance of EU-Prolia to the assessment of biosimilarity. This 3-way PK assessment, together with the 3-way analytical and functional assessment (refer to Section 1.5), justified the relevance of clinical data obtained using EU-Prolia as the comparator (Study HLX14-002-PMOP301) to the assessment of biosimilarity. PK data from Study HLX14-001 also support the conclusion that HLX14 would be expected to have similar PK as US-Xgeva because comparative PK data generated with the 60 mg/1 mL strength are relevant for conclusions about PK similarity for the 120 mg/1.7 mL strength.

Table 6 Summary of statistical analyses for assessment of PK similarity (Study HLX14-001 Part 2)

Parameter	Geometric Mean (%CV)			Geometric Mean Ratio* (90% CI)		
	HLX14 (n=57)	US-Prolia (n=56)	EU-Prolia (n=56)	HLX14 vs U.S.-Prolia	HLX14 vs EU-Prolia	EU-Prolia vs U.S.-Prolia
Primary						
$AUC_{0\text{-}inf}$ (day* µg/mL)	342.0574 (21.5)	355.2415 (24.7)	330.3393 (23.4)	0.97 (0.91, 1.04)	1.04 (0.97, 1.12)	1.07 (0.99, 1.16)
AUC_{last} (day* µg/mL)	331.4480 (21.8)	342.9608 (25.3)	318.1882 (24.1)	0.98 (0.91, 1.05)	1.05 (0.98, 1.13)	1.08 (0.99, 1.16)
Secondary						
C_{max} (µg/mL)	6.041 (17.2)	6.158 (23.1)	5.804 (23.2)	0.99 (0.93, 1.06)	1.05 (0.99, 1.13)	1.06 (0.98, 1.14)

*Presented as percent. Source: FDA analysis

In addition to Study HLX14-001, the applicant also assessed PK/PD similarity in Study HLX14-002-PMOP301, in which post-menopausal women with osteoporosis received a total of 3 subcutaneous injections of 60 mg HLX14 or EU-Prolia (60 mg/mL, once every 6 months), Refer to Section 6.2 for more detailed information on the design of the study. After administration of HLX14 and EU-Prolia, the serum study drug concentration profiles were comparable, with serum concentrations at each timepoint showing consistency between groups across the various treatment periods. A single transition treatment from EU-Prolia to HLX14 did not impact the PK evaluation results.

Study HLX14-001 and HLX14-002-PMOP301 support a demonstration that HLX14 has no clinically meaningful differences from US-Prolia and US-Xgeva. In addition, the incidence of ADAs and NAbs was similar between the treatment arms for each study.

Overall, the submitted clinical pharmacology information supports a demonstration that HLX14 has no clinically meaningful differences from US-Prolia. The evidence contributes to the overall totality of evidence supporting biosimilarity between HLX14 and US-Prolia, and between HLX14 and US-Xgeva.

The clinical pharmacology review team recommends approval of BLA 761444.

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

In the PK similarity study in healthy male subjects (Study HLX14-001), following subcutaneous administration of HLX14, EU-Prolia, U.S.-Prolia, the 90% CIs for the GMRs of HLX14 to EU-Prolia, HLX14 to U.S.-Prolia, , EU-Prolia to U.S.-Prolia for the tested PK parameters (i.e., $AUC_{0\text{-}inf}$, AUC_{last} and C_{max}) were all within the PK similarity acceptance interval of 80%-125%. These pairwise comparisons met the pre-specified criteria for PK similarity between HLX14, EU-Prolia, and U.S.-Prolia; thus, a PK portion of the scientific bridge was established to support the relevance of the clinical data generated using EU-Prolia.

In conclusion, the Applicant provided adequate clinical pharmacology data and information to establish a scientific bridge to justify the relevance of data generated with a non-U.S.- licensed comparator product in Study HLX14-001 to the demonstration of biosimilarity. See sections 1.5, 1.6 and 5.1 details.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

To support a demonstration that HLX14 has no clinically meaningful differences from US-Prolia and US-Xgeva, the Applicant submitted two clinical studies, Studies HLX14-001 and HLX14-002-PMOP301. The Clinical Pharmacology review for this BLA primarily focused on the PK similarity study (Part II of Study HLX14-001) and the additional PK and immunogenicity data from the comparative clinical study (Study HLX14-002-PMOP301). The Applicant collected and analyzed PD data in the 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 HLX14-001

Clinical Pharmacology Study Design Features

Study HLX14-001 was a randomized, single dose, parallel study for comparison of PK, PD, safety, and immunogenicity of HLX14 versus US, EU or CN-Prolia in healthy male subjects. The study was conducted in two parts.

Part I was an open-label, randomized, parallel-controlled, single-dose, pilot study conducted in healthy adult male subjects. In part I, 24 subjects were randomized at a 1:1 ratio to receive a single subcutaneous injection of 60 mg HLX14 or EU-Prolia. The primary objective of Part I was to compare the PK parameters of HLX14 and EU-Prolia to provide a basis for the study design of Part II.

Part II was a double-blinded, randomized, four-arm, parallel-controlled, single-dose, PK similarity study conducted in healthy adult male subjects. In part II, A total of 228 subjects were planned to be enrolled and randomized at a 1:1:1:1 ratio to receive a

single subcutaneous injection of 60 mg HLX14 or US, EU, or CN- Prolia. Randomization was stratified by weight (≤ 65 kg and > 65 kg). The primary objective of Part II was to assess the PK similarity between HLX14 and US, EU and CN-Prolia Secondary objectives included comparisons of pharmacodynamic (PD) responses, safety, tolerability, and immunogenicity.

The subjects were required to take 600 mg of calcium and 400 IU of vitamin D daily after meals during the study (Day 1 - 134) for both Part I and II. This study included three periods: the screening period (28 days), single-dose administration and follow-up period (183 days in part I of the study, 274 days in part II of the study).

Study Population and Treatment

The study was conducted in healthy male, aged > 28 and ≤ 65 years and had a body weight ≥ 50 kg and a BMI ≥ 19 and ≤ 26 kg/m2.

In Part I a total of 155 healthy adult male subjects were screened, of which 24 subjects were enrolled and randomized. 24 (100%) subjects were all treated and completed the study, including 12 subjects in the HLX14 group and 12 subjects in the EU-Prolia group.

In Part II, A total of 1030 healthy adult male subjects were screened, of which 802 subjects failed screening. A total of 228 subjects were enrolled and randomized, with 58 subjects in the HLX14 group, 57 subjects in the US-Prolia group, 56 subjects in the EU-Prolia group, and 57 subjects in the CN-Prolia group. 228 (100%) subjects were all treated, of which 213 (93.4%) subjects completed the study, and 15 (6.6%) subjects discontinued from the study. The reasons for discontinuing from the study were subject's refusal to continue the study (7 subjects, 3.1%), poor compliance and fails to attend follow-up visit in time (6 subjects, 2.6%), and loss to follow-up (2 subjects, 0.9%). There were 4 subjects discontinued from HLX14, US-Prolia and CN-Prolia groups, 3 subjects discontinued from EU-Prolia group.

Overall, 3 subjects were excluded from the PK analysis set because of either early withdrawal or measurable concentrations >5% of C_{max} at pre-dose. Two subjects were excluded from the PD analysis set due to premature drop-out and PD parameters could not be calculated reliably. The distribution of excluded subjects is similar across treatment groups in both analysis sets.

Clinical Pharmacology Study Endpoints

The primary PK endpoints were area under the concentration curve from 0 to last observation/infinity (AUC0-t), area under the serum drug concentration-time curve from time 0 to infinity (AUC0–inf) and maximum observed study drug concentration (Cmax). The PD endpoints were area under the effect-time curve from time 0 to last time (AUEC0-t) of quantifiable concentration of serum C-terminal telopeptide 1 (s-CTX), minimum observed concentration of s-CTX (Imin) and maximum percent inhibition of s-CTX (Imax). To demonstrate PK similarity, the 90% CI of the geometric mean ratios (GMRs) needs to fall within 80-125%. Note, the Applicant calculated the between-group GMRs and their 95% Cis to demonstrate PD similarity, which is considered as exploratory.

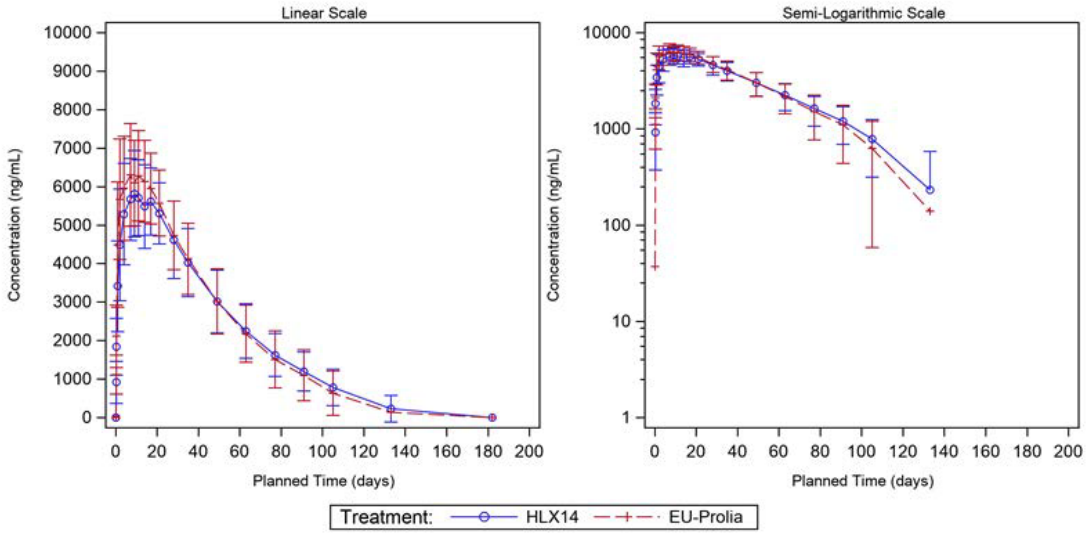
Bioanalytical PK Method and Performance

An ELISA method was used to quantify free study drug in serum of healthy subjects in Study HLX14-001. Free study drug in serum samples was captured by RANKL-His antigen and detected by HRP-conjugated goat anti-human Igκ. After a final wash step, a colorimetric signal produced by tetramethylbenzidine (TMB) reacting with the peroxide is measured at 450 nm with a reference at 630 nm subtracted by plate reader Softmax. The method was fully validated over a range of 148.0 ng/mL to 9864.9 ng/mL for study drug in accordance with the Bioanalytical Method Validation Guidance from the agency. Refer to the Appendix 14.1.1 for more detailed information on method validation.

PK Similarity Assessment

In Part I, the mean study drug serum concentration-time profiles are similar for HLX14 and EU-Prolia (Figure 1).

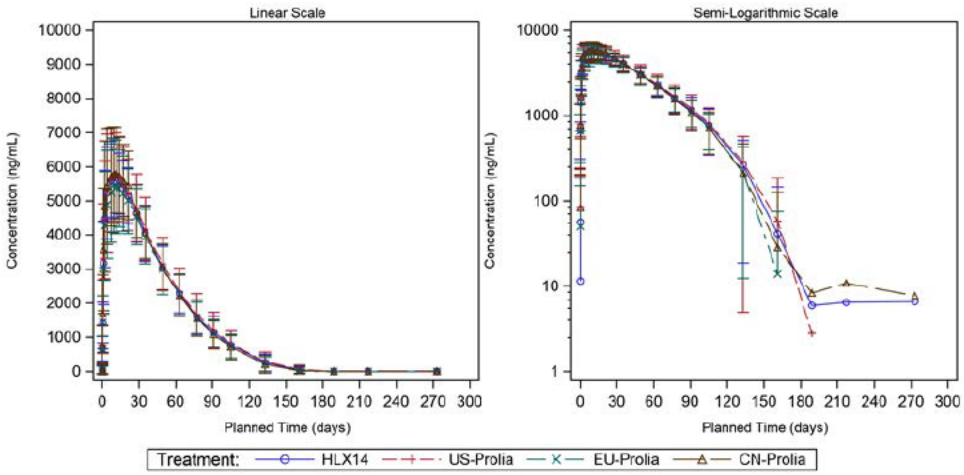
Figure 1 Study drug serum concentrations vs. time profile (Study HLX14-001 Part 1)



Source: Figure 1, page 78, Study HLX14-001 CSR.

In Part II, the mean study drug serum concentration-time profiles are similar for all treatment groups (Figure 2). For the primary PK parameters ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and Cmax), the similarity criterion (90% CI of the geometric least-square mean ratio for test/reference within the limits 80.00% and 125.00%) was met in all the comparisons (Table 7).

Figure 2 Study drug serum concentrations vs. time profile (Study HLX14-001 Part 2)



Source: Figure 2, page 79, Study HLX14-001 CSR.

Table 7: Geometric mean ratio and 90% CI for primary PK parameters to compare treatments (Study HLX14-001)

PK parameter (unit)	T vs R	GeoLSM n	GeoLSM T	GeoLSM n	GeoLSM R	T/R Ratio	90% CI of T/R Ratio	interindividual variability (%)
$AUC_{0\text{-}inf}$ (day*µg/mL)	HLX14 vs US-Prolia®	57	335.00	56	344.86	0.97	0.91, 1.04	22.88
	HLX14 vs EU-Prolia®	57	335.00	54	321.32	1.04	0.97, 1.12	22.45
	HLX14 vs CN-Prolia®	57	335.00	55	336.20	1.00	0.93, 1.06	20.96
$AUC_{0\text{-}t}$ (day*µg/mL)	HLX14 vs US-Prolia®	57	324.41	56	332.62	0.98	0.91, 1.05	23.22
	HLX14 vs EU-Prolia®	57	324.41	54	308.97	1.05	0.98, 1.13	23.02
	HLX14 vs CN-Prolia®	57	324.41	55	323.68	1.00	0.94, 1.07	21.33
C_{max} (µg/mL)	HLX14 vs US-Prolia®	57	5.95	56	5.99	0.99	0.93, 1.06	20.99
	HLX14 vs EU-Prolia®	57	5.95	56	5.65	1.05	0.99, 1.13	21.15
	HLX14 vs CN-Prolia®	57	5.95	56	6.13	0.97	0.91, 1.04	20.74

Note: Due to $\%AUC_{ex}$ of subjects (b) (6) being greater than 20%, the related PK parameters $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ were not included in equivalence evaluations.
$AUC_{0\text{-}inf}$= area under the serum drug concentration-time curve from time 0 to infinity; $AUC_{0\text{-}t}$= area under the serum drug concentration-time curve from time 0 to the last concentration-quantifiable time t; C_{max}= maximum serum drug concentration.

Source: Table 15, page 85, Study HLX14-001 CSR.

Bioanalytical PD Method and Performance

CTX levels in human serum were quantified using the Roche Cobas 6000 e601 Immunoassay Analyzer. In this assay, samples were incubated with biotinylated monoclonal anti-β-CrossLaps antibody. β-CrossLaps present in the samples was captured by biotinylated monoclonal anti-β-CrossLaps antibody. Ruthenium complex-labeled monoclonal anti-β-CrossLaps antibody was then used to detect β-CrossLaps. When voltage was applied, the ruthenium complex induces chemiluminescent emission. The resulting chemiluminescent emission was measured by a photomultiplier and the results were derived from an instrument-specific calibration curve, generated through a two-point calibration and incorporated into the reagent barcode data.

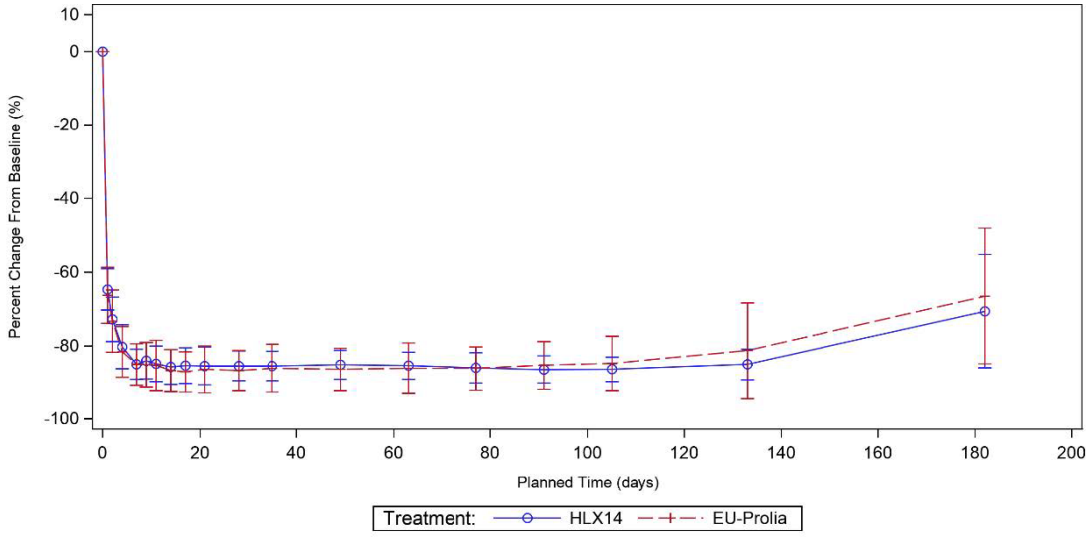
All validation parameters passed the acceptance criteria, and the assays are considered appropriate for the quantification of CTX human serum. The validated range of CTX measurement is 0.01 ng/mL to 6.00 ng/mL.

PD Similarity Assessment

The Applicant collected and analyzed PD data in the 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.

In Part I of Study HLX14-001, after a single dose of HLX14 and EU-Prolia, the profiles of percentage change from baseline in s-CTX concentration basically coincided, the s-CTX concentration-time profiles are similar for HLX14 and EU-Prolia (Figure 3).

Figure 3 Mean Percent Changes from Baseline in s-CTX Concentration vs. time profile (Study HLX14-001 Part I)



Source: Figure 4, page 91, Study HLX14-001 CSR.

For the PD parameter In Part II, the range of 95% CIs for GMRs of key PD parameters (Imax and AUEC0-t) was 0.89 to 1.16 in the 6 pairs. Imin of HLX14, US-Prolia, EU-Prolia and CN-Prolia was also comparable (Table 8)

Table 8 Summary of Pharmacodynamic Parameters for Similarity by Treatment (Study HLX14-001 Part 2)

PD parameter (unit)	T vs R	GeoLSM n	GeoLSM T	GeoLSM n	GeoLSM R	T/R Ratio	95% CI of T/R Ratio
$AUEC_{0-t}$ (day*%inhibition)	HLX14 vs US-Prolia®	58	18742.05	56	19303.09	0.97	0.91, 1.03
	HLX14 vs EU-Prolia®	58	18742.05	56	18013.93	1.04	0.96, 1.13
	HLX14 vs CN-Prolia®	58	18742.05	56	18372.14	1.02	0.96, 1.09
I_{min} (ng/mL)	HLX14 vs US-Prolia®	58	0.05	56	0.05	0.97	0.82, 1.16
	HLX14 vs EU-Prolia®	58	0.05	56	0.05	0.97	0.81, 1.15
	HLX14 vs CN-Prolia®	58	0.05	56	0.05	0.94	0.79, 1.11
I_{max} (%inhibition)	HLX14 vs US-Prolia®	58	89.47	56	90.88	0.98	0.97, 1.00
	HLX14 vs EU-Prolia®	58	89.47	56	89.82	1.00	0.98, 1.02
	HLX14 vs CN-Prolia®	58	89.47	56	89.67	1.00	0.98, 1.02

$AUEC_{0-t}$= Area under the effect-time curve from time 0 to last time of quantifiable concentration of s-CTX; I_{max}= maximum percent inhibition of s-CTX; I_{min}= minimum observed concentration of s-CTX; T_{min}= time to reach I_{min} of s-CTX.
Source: Table 21, page 95, Study HLX14-001 CSR.

5.3.2. STUDY HLX14-002-PMOP301

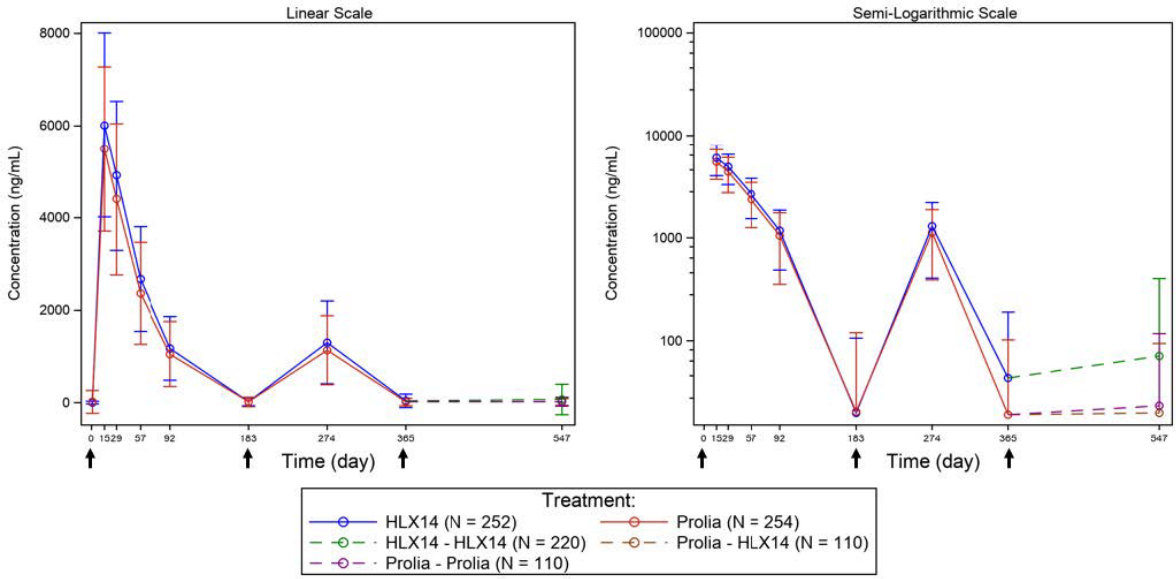
Study HLX14-002-PMOP301 is a randomized, double-blind, international multicenter, parallel-controlled phase III clinical study to compare the efficacy, PD, safety, PK and immunogenicity of HLX14 vs.EU-Prolia in postmenopausal women with osteoporosis at high risk of fracture. In treatment period 1, patients were randomized in a 1:1 ratio to receive either HLX14 or EU-Prolia subcutaneously at Day 1 (D1) and Day 183 (D183). Blood samples for PK were collected on weeks 0, 2, 4, 8, 13, 26, 39, 52 and 78. Blood samples for immunogenicity were collected on weeks 0, 2, 4, 8, 13, 26, 39, 52, 54, 65 and 78.

Following this, in treatment 2, on day 365, patients who received EU-Prolia in the period 1 were re-randomized in a 1:1 ratio to either continue with a third dose of EU-Prolia (Prolia/Prolia group) or transit to a single dose of HLX14 as their third dose of study drug (Prolia/HLX14 group), Patients who received HLX14 in the period 1 continued to receive HLX14, but they also followed the randomization procedure to maintain blinding. Patients were followed up to day 546. (Refer to Section 6.2. for more detailed information on the design of the study).

PK Assessment

A total of 514 patients were included in the PK analysis dataset (256 patients from the HLX-14 and 258 patients from the EU-Prolia treatment groups). The mean study drug concentration-time profiles are similar between HLX14 and EU-Prolia (Figure 4)

Figure 4 Study drug serum concentrations vs. time profile (Study HLX14-002-PMOP301)



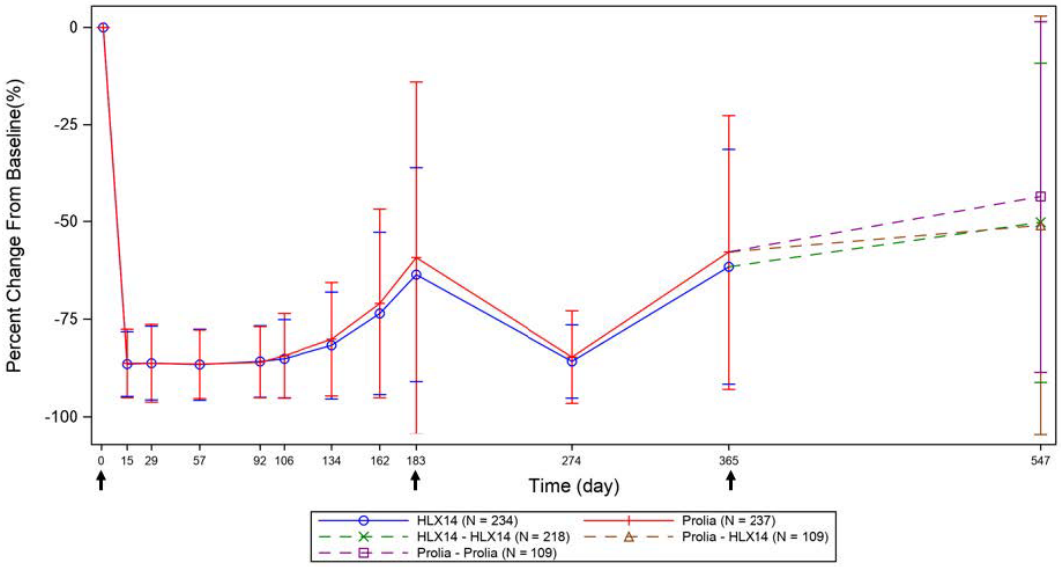
↑: receiving the study treatment.
N for D0-365: Number of subjects in the Pharmacokinetic Set.
N for D365-547: Number of subjects in the Pharmacokinetic Set and receiving the third dose.
Source: Figure 11-8, page 173, Study HLX14-002-PMOP301 CSR.

PD Assessment

Serum CTX and procollagen type I N-terminal propeptide (P1NP) concentrations were analyzed by treatment group and visit. Blood samples for PD were collected at weeks 0, 2, 4, 8, 13, 15, 19, 23, 26, 39, 52, and 78 (end of the study visit).

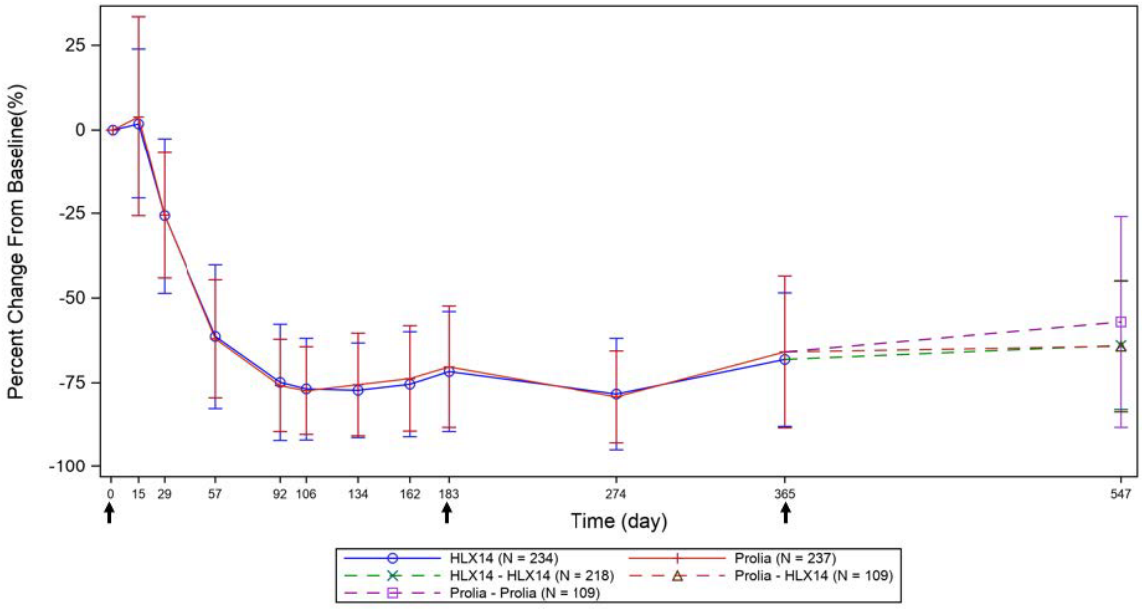
Mean percent changes from baseline in s-CTX and P1NP over the complete study period are shown in Figure 5 and Figure 6, respectively. The PD profiles for both markers are similar between HLX14 and EU-Prolia treatment groups both before and after the single transition treatment.

Figure 5 Mean(±SD) for Percent Change from Baseline to Week 78 in s-CTX (Study HLX14-002-PMOP301)



↑: receiving the study treatment.
N for D0-365: Number of subjects in the PDS analysis set.
N for D365-547: Number of subjects in the PDS analysis set and receiving the third dose.
Source: Figure 11-6, page 164, Study HLX14-002-PMOP301 CSR.

Figure 6 Mean(±SD) for Percent Change from Baseline to Week 78 in s-P1NP (Study HLX14-002-PMOP301)



↑: receiving the study treatment.
N for D0-365: Number of subjects in the PDS analysis set.
N for D365-547: Number of subjects in the PDS analysis set and receiving the third dose.
Source: Figure 11-7, page 167, Study HLX14-002-PMOP301 CSR.

5.4. Clinical Immunogenicity Studies

5.4.1. STUDIES HLX14-001 and HLX14-002-PMOP301

Design features of the clinical immunogenicity assessment

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

Immunogenicity endpoints

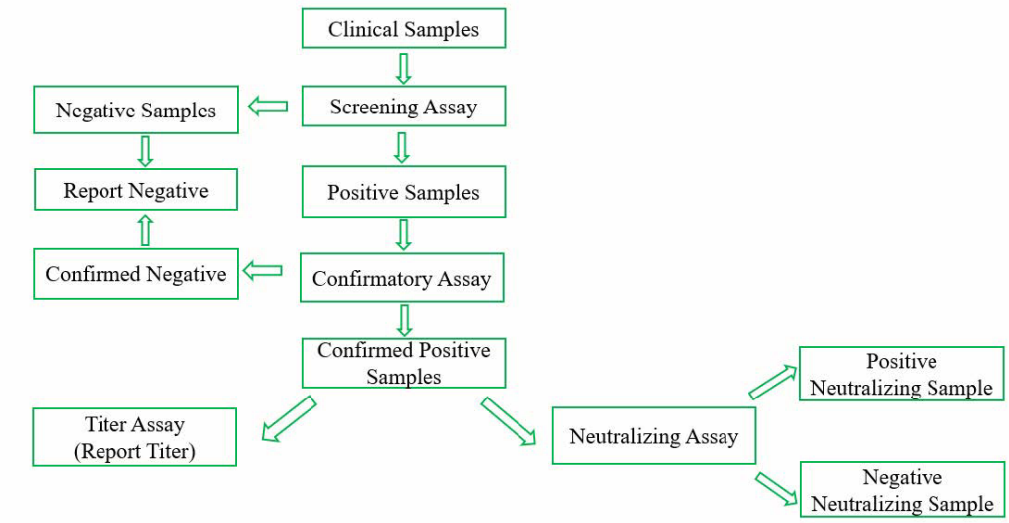
Immunogenicity assessment was proposed as the secondary study endpoints in the following studies:

Study HLX14-001 and Study HLX14-002-PMOP301: Positive rate of anti-drug antibody (ADA) and neutralizing antibody (NAb) to the study drugs.

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.

Anti-drug antibodies (ADA) against study drugs/HLX14 in human serum were detected using an electro-chemiluminescent (ECL) method. Samples collected from study HLX14-001 and HLX14-002-PMOP301 were analyzed with a multi-tiered approach (Figure 7). In both studies, a three-tier approach was applied, including screening, confirmatory, and followed by neutralizing antibody titration. Subsequently, the neutralizing ability of confirmed ADA positive samples was characterized.

Figure 7 Tiered Approach in the HLX14 Anti-drug Antibody, Neutralizing Antibody and Titer Assays



Source: Figure 1, page 14, Integrated Summary of Immunogenicity

Additionally, In Study HLX14-001 and HLX14-002-PMOP301, the range of serum concentration of study drugs (HLX14 or Prolia) for all treatment groups (< 12 mcg/mL) is significantly lower to the drug tolerance of the ADAs/NAbs assay (45 µg/mL), indicating minimal interference with the ADAs/Nabs assay in the presence of study drugs in the serum at different sampling timepoints.

Refer to OPQA3's 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 HLX14-001 Part I, ADA samples were collected at pre-dose, Days 29, 64, 106, 183 post-dose. In Study HLX14-001 Part II, ADA samples were collected at pre-dose, Days 15, 29, 64, 106, 190, 274 post-dose. In Study HLX14-002-PMOP301, ADA samples were collected at pre-dose, Days 15, 29, 57, 92, 183, 274, 365, 379, 456 and 547 post-dose.

The immunogenicity assessment schedules in Studies HLX14-001 and HLX14-002-PMOP301 are deemed appropriate. These schedules include ADA sampling at baseline (pre-dose) and at multiple post-dose timepoints, extending beyond 5 half-lives of study drugs. This comprehensive sampling strategy allows for a thorough evaluation of the immunogenic response over time.

Furthermore, the study design incorporates concurrent measurement of drug concentrations at the same timepoints as immunogenicity sample collection. This parallel assessment of drug levels and ADA formation enhances the ability to interpret the immunogenicity data in 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)

In part I of study HLX14-001, after a single dose of HLX14 or EU-Prolia in healthy subjects, there was no positive ADA result observed for any subject at any time.

The incidence of ADA and NAb in studies HLX14-001 (part 2) and HLX14-002-PMOP301 are shown in Table 9, Table 10, and Table 11, respectively.

The incidence of ADAs and NAbs was low and comparable between treatment groups for each study. There was 1 NAb detected in all treatment groups in Study HLX14-001. The incidence of NAbs was low in all treatment groups in Study HLX14-002-PMOP301. Pretreatment of US-Prolia and transitioning to HLX14 did not influence the incidence of ADAs and NAbs in HLX14 group after the transition (Table 9).

Table 9 Immunogenicity results for binding ADA and NAb in Study HLX14-001 (Part 2).

	N	Anti-Drug antibody		NAb
		Baseline	Treatment-Induced	
HLX14	58	1/58 (1.7%)	6/58 (10.3%)	0/58 (0)
US-Prolia	57	1/57 (1.8%)	10/57 (17.5%)	1/57 (1.8%)
EU-Prolia	56	3/56 (5.4%)	13/56 (23.2%)	0/56 (0)

Source: Table 22 Page 97, Study HLX14-001 CSR.

Table 10 Immunogenicity results for binding ADA and NAb in Study HLX14-002-PMOP301Treatment Period 1 (from baseline to Week 52).

	N	Anti-Drug antibody		NAb
		Baseline	Treatment-Induced	
HLX14	256	14/256 (5.5%)	28/256 (11.1%)	0/256 (0)
EU-Prolia	258	17/258 (6.6%)	35/258 (13.8%)	2/225 (0.8%)

Source: Table 11-23 Page 174, HLX14-002-PMOP301 CSR.

Table 11 Immunogenicity results for binding ADA and NAb in Study HLX14-002-PMOP301, Treatment Period 2 (Week 52-78).

	N	Anti-Drug antibody	NAb
HLX14/HLX14	220	28/220 (12.7%)	0/220 (0)
EU-Prolia/EU-Prolia	110	15/110 (13.6%)	1/110 (0.9%)
EU-Prolia/HLX14	110	17/110 (15.5%)	1/110 (0.9%)

Source: Table 11-24, Page 175, Study HLX14-002-PMOP301 CSR.

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

In part 1 of Study HLX14-001, no ADA positive and ADA negative subgroup analysis was performed as none of the samples were found to be ADA positive.

In studies HLX14-001 (part 2) and HLX14-002-PMOP301, the impact of ADAs on the PK of the study drug was evaluated per treatment group and ADA status (subjects with at least one ADA-positive sample and ADA-negative subjects) by comparing $AUC_{0\text{-inf}}$,

$AUC_{0\text{-last}}$ and C_{max} values. All PK parameters were similar in ADA-positive and ADA-negative subjects, across all treatment groups in studies HLX001-14 Part II (Table 12) and HLX14-002-PMOP301 (Table 13 and Table 14) indicating that there was no significant impact of immunogenicity on the PK of the studied drugs.

Further, in Study HLX14-002-PMOP301, PK was not impacted by immunogenicity following a single transition from EU-Prolia to HLX14.

Table 12 Descriptive Statistics of Study Drug PK Parameters by ADA Result in Study HLX14-001 Part 2

PK Parameter (Unit)	Mean±SD (CV%)							
	HLX14 (N=57)		US-Prolia® (N=56)		EU-Prolia® (N=56)		CN-Prolia® (N=56)	
	ADA Positive (N=6)	ADA Negative (N=51)	ADA Positive (N=10)	ADA Negative (N=46)	ADA Positive (N=13)	ADA Negative (N=43)	ADA Positive (N=12)	ADA Negative (N=44)
$AUC_{0\text{-inf}}$ (day*µg/mL)	335.4887± 69.6158 (20.8)	342.8302± 74.7572 (21.8)	387.9709± 88.6052 (22.8)	348.1264± 87.0739 (25.0)	319.8410± 58.4472 (18.3)	333.6680± 82.6193 (24.8)	330.2863± 60.4909 (18.3)	347.0535± 76.4838 (22.0)
$AUC_{0\text{-t}}$ (day*µg/mL)	324.9522± 71.5933 (22.0)	332.2122± 73.0125 (22.0)	372.3359± 84.7523 (22.8)	336.5749± 86.6557 (25.7)	308.0581± 59.3831 (19.3)	321.4002± 81.6165 (25.4)	317.8469± 58.9879 (18.6)	334.4889± 74.8523 (22.4)
C_{max} (µg/mL)	5.760±1.0206 (17.7)	6.074±1.0492 (17.3)	6.445±1.4523 (22.5)	6.095±1.4221 (23.3)	5.819±1.3486 (23.2)	5.799±1.3645 (23.5)	6.489±1.7143 (26.4)	6.237±1.4005 (22.5)

Note: Due to $\%AUC_{ex}$ of subjects (b) (6) were greater than 20%, these subjects' PK parameters $AUC_{0\text{-inf}}$ and $AUC_{0\text{-t}}$ were not included in summary and equivalence evaluation, but listed. Subject (b) (6) EU-Prolia® group, ADA negative; Subject (b) (6) CN-Prolia® group, ADA positive.

Source: Table 23, Page 99, Study HLX14-001 CSR

Table 13 Study Drug Serum Concentrations (ng/mL) from Baseline to Week 52 by ADA Result in Study HLX14-002-PMOP301

Nominal Time Point	Statistic	HLX14 (N = 252)		EU-Prolia® (N = 254)	
		ADA Positive	ADA Negative	ADA Positive	ADA Negative
D1 pre-dose	n	28	224	35	219
	n of BLQ	27	223	35	215
	Mean	12.6679	1.4951	0	22.8685
D15	n	22	174	32	159
	Mean	6062.9030	6004.6582	5514.5714	5482.0757
	CV%	40.2	32.3	35.2	32.1
D29	n	26	204	34	195
	Mean	5278.4377	4864.5690	4245.9443	4431.8026
	CV%	38.4	32.0	38.6	37.2
D57	n	26	189	31	189
	Mean	2548.9087	2687.7537	2310.5763	2371.8341
	CV%	51.1	41.2	54.5	45.4
D92	n	27	191	31	186
	Mean	1186.8113	1170.4090	995.1599	1062.0501
	CV%	66.6	57.3	73.0	65.3
D183 pre-dose	n	28	206	33	204
	n of BLQ	25	192	32	190
	Mean	29.4846	18.7670	17.2444	21.1524
	CV%	304.9	458.7	-	473.6
D274	n	27	195	33	200
	Mean	1365.5957	1295.5978	1178.4753	1126.4652
	CV%	93.5	64.3	87.0	61.2
D365 pre-dose	n	28	196	32	198
	n of BLQ	23	173	29	186
	Mean	74.1165	39.6330	36.5114	16.5214
	CV%	257.0	355.2	377.7	428.8
Discontinuation[1]	n	0	0	1	0
	n of BLQ	-	-	1	-
	Mean	-	-	0	-

BLQ: Below the lower limit of quantification.
[1] Discontinuation summarized the early terminated subjects' tests results at their end of study visit, these subjects did not take the third dose on week 52.
Source: Table 1, Page 3, Response to information request email dated Oct 24, 2024

Table 14 Study Drug Serum Concentrations (ng/mL) from Week 52 to Week 78 by ADA Result in Study HLX14-002-PMOP301

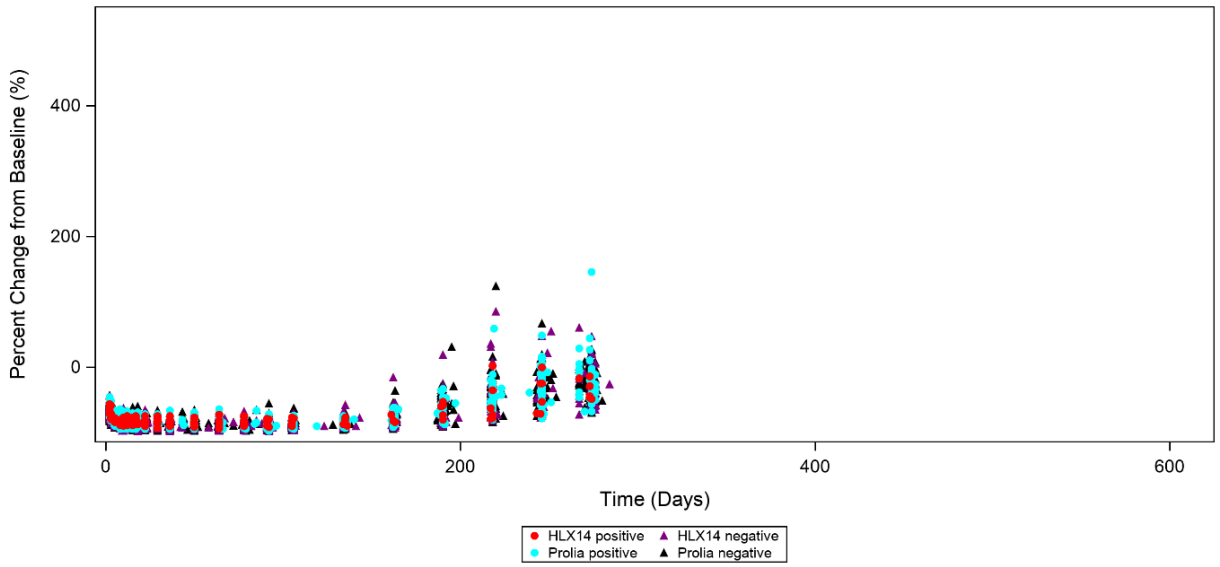
Nominal Time Point	Statistic	HLX14/HLX14 (N = 220)		EU-Prolia®/HLX14 (N = 110)		EU-Prolia®/EU-Prolia® (N = 110)	
		ADA Positive	ADA Negative	ADA Positive	ADA Negative	ADA Positive	ADA Negative
D365 pre-dose	n	28	190	17	91	15	93
	n of BLQ	23	169	16	88	13	85
	Mean	74.1165	38.6685	10.0904	7.4756	66.4552	24.7793
D547	n	28	188	17	90	14	93
	Mean	75.4706	71.0340	44.0695	15.5846	13.8093	25.0306
	CV%	202.3	490.7	228.3	437.0	-	396.2

N: Number of subjects in the Pharmacokinetic Set and receiving the third dose.
BLQ: Below the lower limit of quantification.
Source: Table 2, Page 4, Response to information request email dated Oct 24, 2024

Impact of ADA and NAb on Efficacy

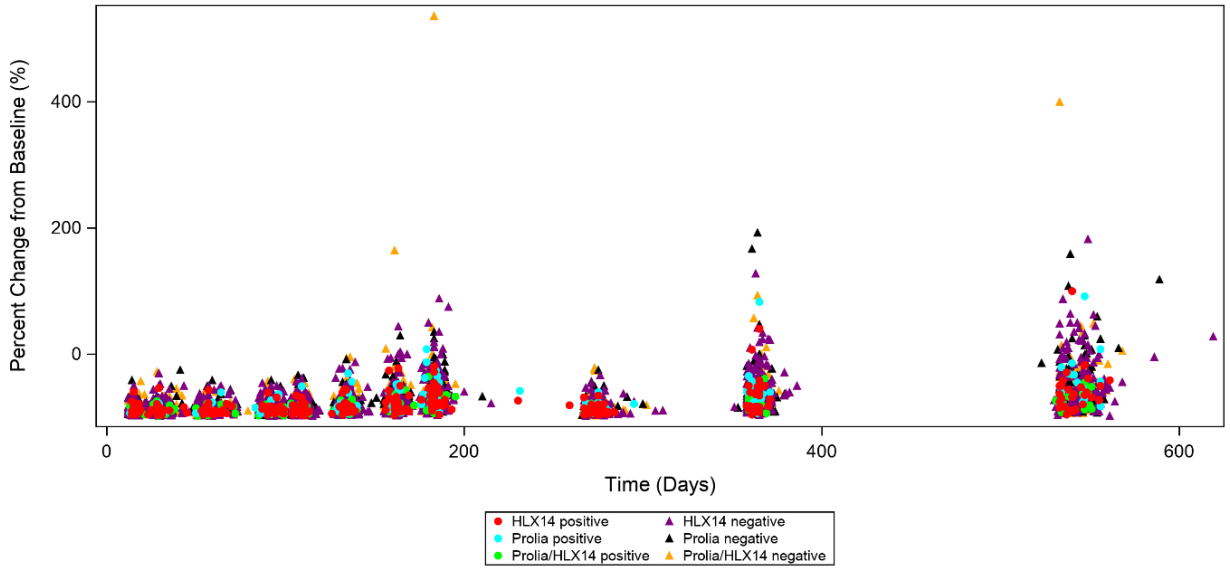
The impact of ADAs on PD of study drug was evaluated in Study HLX14-001 Part II (Figure 8) and HLX14-002-PMOP301 (Figure 9) by comparing the percentage change from baseline in s-CTX concentration by treatment group and ADA result. In both studies, the profiles of percent changes from baseline to Week 78 in s-CTX concentration were superimposable for ADA-positive and ADA-negative subjects, indicating that there was no clinically significant impact of immunogenicity on the PD of the studied drugs.

Figure 8 Percent Change from Baseline in s-CTX Concentrations by ADA in Study HLX14-001 Part II



Source: Figure 2.7.2-10, Page 40, Summary of Clinical Pharmacology Studies.

Figure 9 Percent Change from Baseline in s-CTX Concentrations by ADA in Study HLX14-002-PMOP301



Source: Figure 2.7.2-11, Page 41, Summary of Clinical Pharmacology Studies

Impact of ADA and NAb on Safety

The review of immunogenicity as it pertains to safety can be found in Section 6.4. There was no correlation between clinical immunogenicity and antibody status.

Authors:

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

The comparative clinical study in post-menopausal women with osteoporosis consisted of two treatment periods: treatment period 1 (from baseline to Week 52) and treatment period 2 (from Week 52 to Week 78). In treatment period 1, subjects were randomized in a 1:1 ratio to either HLX14 or EU-Prolia. The treatment period 2 was a single transition period, in which subjects assigned to EU-Prolia in treatment period 1 were re-randomized to receive a third dose of either Prolia or HLX-14.

The primary analysis was performed after all subjects completed the study visit of Week 52. Based on the results of the two one-sided tests, both the lower and upper confidence limits of the difference in primary endpoint fell entirely within the pre-specified equivalence margins of +/-1.45% (see Section 6.2.1 of this review). This indicated that the difference between the HLX14 group and the EU-Prolia group was not

clinically meaningful, thereby showed that the two products were similar with respect to efficacy.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the statistical and clinical analyses.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

6.2.1. HLX14-002-PMOP301

Data and Analysis Quality

There are no concerns regarding data quality and integrity.

Study Design and Endpoints

The study was a randomized, double-blind, international, multicenter, parallel-controlled clinical study consisting of two treatment periods.

The study was conducted in China and Australia. A total of 40 study sites (including one site in Australia) enrolled subjects. Two subjects were enrolled from one site in Australia.

A total of 514 subjects were randomized into two groups for treatment period 1 (from baseline to Week 52): 256 subjects in the HLX14 group and 258 subjects in the EU-Prolia group. Two stratification factors (BMI (kg/m^2) [<25, 25-30, >30] and geographic region [Asian or non-Asian]) were used in this study. For treatment period 2 (from Week 52 to Week 78), 220 subjects from Prolia group were re-randomized into two groups: 110 subjects to the EU-Prolia/HLX14 group and 110 subject to the EU-Prolia/EU-Prolia group; 220 subjects in the HLX14 group continued into the HLX14/HLX14 group without re-randomization.

Subjects who were ambulatory postmenopausal women with osteoporosis aged 60 to 90 years (both inclusive) were included in the study. Refer to Section 9.3 of the Clinical Study Report (CSR) for a complete list of inclusion/exclusion criteria.

The study included a screening period, a treatment period (treatment period 1 and treatment period 2), and an end-of-study visit.

Screening period (from Day -28 to Day -1): Subjects who met all inclusion criteria and did not meet any exclusion criteria were randomly assigned into either the HLX14 or the Prolia in a 1:1 ratio. Vitamin D and calcium supplementation were allowed during the screening period.

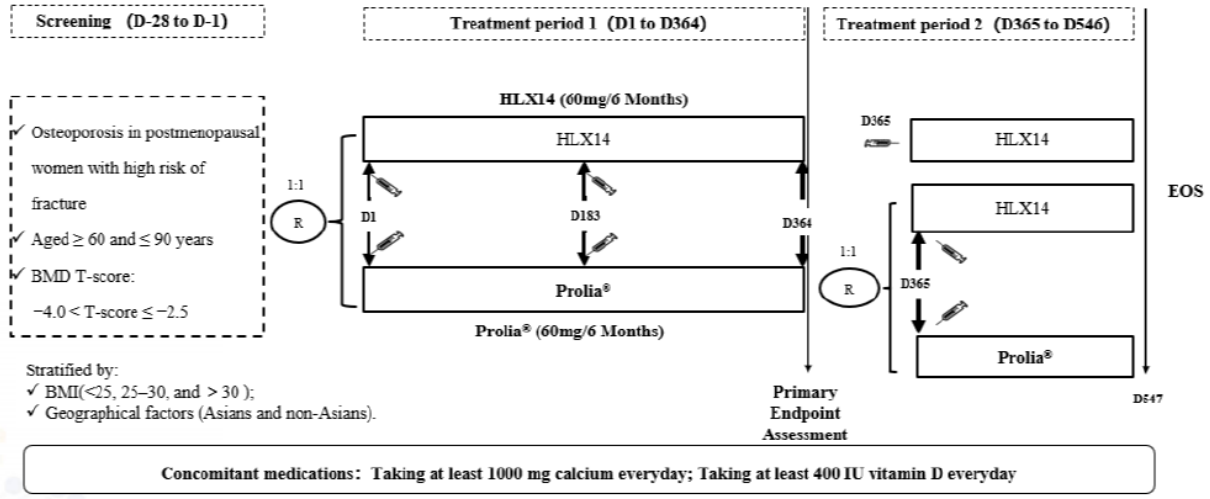
Treatment period: In treatment period 1 (Day 1 to Day 364), subjects received 60 mg subcutaneous injection of either HLX14 or EU-Prolia on Day 1 and Day 183. Following this, in treatment period 2 (Day 365 to Day 546) , on Day 365, subjects in the Prolia group were re-randomized in a 1:1 ratio to either continue with a third dose of Prolia

(Prolia/Prolia group) or transit to a single dose of HLX14 as their third dose (Prolia/HLX14 group), while subjects in the HLX14 groups continued to receive a third dose of HLX14 (HLX14/HLX14 group). Throughout the study, all subjects were required to take at least 1000 mg of calcium and at least 400 IU of vitamin D daily with dosage adjustments made by the Investigator based on serum calcium levels.

End-of-study (EOS) visit: The end-of-study visit was performed at the end of the study (Day 547) or at premature withdrawal.

Refer to Figure 10 for the study design scheme:

Figure 10: Study design scheme for Study HLX14-002-PMOP301



[Source: Section 1.2 of the Protocol v5.0]

Dosage and administration for HLX14 or Prolia: 60 mg, single subcutaneous injection at the thigh, abdomen, or upper arm, administered once every 6 months (Q6M), 3 doses in total. No dose adjustment was permitted.

Blinding

Neither the Investigators, subjects nor applicable study staff were aware of which medication the subject was receiving. Blinded state remained until study completion and database lock.

Efficacy variables

Primary efficacy endpoint

- Percent change from baseline in BMD at the lumbar spine to Week 52, assessed by the central imaging

Secondary efficacy endpoints

- Percent changes in BMD at the lumbar spine from baseline to Week 26, Week 52, Week 78 (assessed by Investigator)

- Fracture rate from baseline to Week 52, Week 78
- Percent changes in BMD at the lumbar spine from baseline to Week 26, Week 78 (assessed by the central imaging)
- Percent changes in BMD at the total hip from baseline to Week 26, Week 52 and Week 78 (assessed by the central imaging and Investigator)
- Percent changes in BMD at the femoral neck from baseline to Week 26, Week 52 and Week 78 (assessed by the central imaging and Investigator)

Note that the statistical review focuses on the assessment of treatment effect in treatment period 1.

Statistical Methodologies

Efficacy analysis procedures were prespecified in the protocol and the Statistical Analysis Plan (SAP). The prespecified analysis procedures were generally consistent with the FDA's recommendations provided during the IND stage except for the method to handle missing primary endpoint for the primary analysis.

Statistical hypotheses

The null and the alternative hypotheses for assessing similarity between the test and reference products were as follows:

H_0: $|\mu_{HLX14} - \mu_{Prolia}| \geq \Delta$

H_1: $|\mu_{HLX14} - \mu_{Prolia}| < \Delta$,

where μ_{HLX14} and μ_{Prolia} represented the mean of the improvement percentage in lumbar spine BMD from baseline to Week 52 in the HLX14 group and the Prolia group, respectively, and Δ represented a margin of 1.45%. The margin was based on a meta-analysis of three historical studies and agreed upon by the FDA. The margin was selected to preserve at least 70% of the treatment effect of the reference product.

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%.

Analysis set

Intent-to-treat (ITT) set: Defined as all postmenopausal women with osteoporosis at high risk of fracture who were randomized in this study. The primary efficacy analysis is based on the ITT set.

Per protocol set (PPS): A subset of ITT set. The PPS consisted of all subjects randomized without major protocol deviations that significantly affected the primary efficacy assessment. Major protocol deviation included deviation from visit schedule, inclusion/exclusion criteria, procedures/tests, disallowed medications, and treatment administration. As a supportive analysis, the analysis based on the PPS complemented the analysis based on the ITT set.

Safety Set (SS): Defined all subjects who received at least one dose of the study drug. The SS was the primary analysis set for safety measures and was analyzed based on the actual treatment groups.

There were protocol deviations related to COVID-19 during treatment period 1 in the ITT set, these deviations were due to visit schedule, procedures/test (refusing relevant examination), and investigational product (IP) administration/treatment (poor compliance). None of them applied to withdrawal or inclusion/exclusion criteria.

Intercurrent events (ICEs)

There were 4 types of intercurrent events (ICEs) considered in the study. Each type of ICEs and the corresponding subcategories are listed below (also in Table 9-7 of CSR for additional information):

- Premature treatment discontinuation before Week 26
    - Treatment discontinuation due to adverse event (AE) (related to treatment)
    - Treatment discontinuation due to lack of efficacy (related to treatment)
    - Treatment discontinuation for other reasons (not related to treatment)
- Bone-affecting interventions
    - Use of prohibited drugs
    - Non-drug intervention (including but not limited to bilateral oophorectomy)
- AEs affecting bone
    - Injury, poisoning and procedural complications: spinal fracture, hip fracture and so on.
    - Metabolism and nutrition disorders/endocrine disorders: diabetes mellitus (new-onset), hyperthyroidism and so on
    - Gastrointestinal disorders: Crohn's disease, ulcerative colitis and so on.
    - Musculoskeletal and connective tissue disorders: rheumatoid arthritis, ankylosing spondylitis and so on.
    - Nervous system disorders: Parkinson's disease, spinal cord injury and so on.
    - Other: chronic obstructive pulmonary disease, HIV infection and so on.
- Changes in concomitant medication
    - Changes in concomitant medication: thiazolidinedione, GLP-1 and so on

For lumbar spine fracture that occurred early, such as 30 days after the first dose, the Applicant considered the occurrence of fractures could be independent of efficacy, and the missing primary endpoint value was multiple imputed under missing at random (MAR) assumption. For subjects who did not take the second injection due to AE or lack of efficacy, and for treatment related lumbar spine fractures, the values after these ICEs

were imputed by the worst value collected from the corresponding subject before the ICE happened (worst-observation-carried-forward or WOCF).

If subjects took prohibited drug and had an impact on efficacy, the efficacy data collected after ICEs occurred were not used for analysis even if subjects took 2 doses according to the protocol, and the missing values were multiply imputed under MAR assumption. The ICEs such as non-drug intervention, adverse events affecting bone, and changes in concomitant medication were treated in the same way as use of prohibited drugs.

Other missing data were multiply imputed under MAR assumption. Missing data at Week 26 and Week 52 were imputed sequentially using the regression imputation model with baseline BMD, BMD at Week 26, and BMD at Week 52, baseline BMI (kg/m^2) (<25, 25-20, >30) as terms in the model, by treatment group. A total of 200 datasets with imputed values were generated.

Statistical analysis method

The analysis model for percent change in BMD was an analysis of covariance (ANCOVA) model with treatment and BMI category (<25, 25-30, >30) as factors and baseline BMD as a covariate. Adjusted means of percent change in BMD in the two groups and the difference between the two groups with 2-sided 90% confidence interval were calculated.

It was recommended to include stratification factors in the ANCOVA model for the primary analysis. However, one of the stratification factors, race, was not included in the model. It is reasonable to exclude race from the ANCOVA model because all study subjects were Asian (Chinese), except for two white subjects from Australia.

A total of 200 complete datasets after imputation was analyzed using the ANCOVA model and the results were combined using Rubin's rule.

Sensitivity analysis

- Mixed model for repeated measures (MMRM): The same strategy was applied to handle the ICEs for the primary analysis. The MMRM model including treatment, BMI stratification factor, visit, and visit by treatment interaction as factors, and baseline BMD as a covariate was used to calculate the adjusted means, standard errors, the difference between the two groups with 2-sided 90% CI and 95% CI. An unstructured covariance matrix was used to model the covariance structure.
- Tipping point analysis: Missing data (including those values excluded from analyses due to ICEs) were first imputed based on MAR. Secondly, for each group a penalty was added to the imputed values at Week 52 when ICEs (premature treatment discontinuation before Week 26 due to any reason, use of prohibited drugs and treatment related lumbar spine fractures) occurred. The approach was to gradually increase the penalty until the BMD conclusion from the primary analysis was changed. The specific penalty value that changed the conclusion was used to evaluate the robustness of the primary analysis results.

- Treatment policy: Week 52 data collected after ICEs were used. The MMRM model was used.
- Add covariate: The same strategy was used to handle the ICEs with the primary analysis. Added age (<65 years, ≥65 years) and prior bisphosphonate use (Yes/No) in the multiple imputation and the ANCOVA. Also presented the results of using treatment policy and the MMRM model with added covariates.

Secondary efficacy endpoints

There were no key secondary efficacy endpoints defined in this study. The applicant listed secondary efficacy endpoints, however, there were no statistical testing plans for these endpoints.

Statistics Information Request (IR)

The information request (IR) was sent out to the Applicant, and one of the requested information in the IR letter was to redo the primary analysis implementing two one-sided tests with missing data imputed under the corresponding null hypothesis. The Applicant submitted response (dated on October 22, 2024). The response had information requested in the IR letter as well as new primary results implementing the two one-sided tests. The two one-sided tests that the Applicant submitted:

- For testing non-inferiority, missing observations were imputed based on missing at random and imputed values for the HLX14 were worsen by a non-inferior margin 1.45%.
- For testing non-superiority, missing observations were imputed based on missing at random and imputed values for the HLX14 were increased by a non-superior margin 1.45%.

However, the proposed imputation approach is not identical to FDA's recommended imputation under the null method. FDA's preferred method is to impute missing data using the observed Prolia data first and then shift the imputed values in the HLX14 group by the margin before performing the two one-sided tests.

Subgroup analysis

Based on the ITT set, for Treatment Period 1, primary efficacy endpoint was summarized for the following subgroups:

- Age (<60, 60-85, >85)
- Age (<65, ≥65)
- BMI (<25, 25-30, >30)
- Geographic region (Asian or no-Asian)
- Prior use of bisphosphonates (Y/N)
- Smokers (non-smoker, light smoker, other)

Subject Disposition

A total of 1078 subjects were screened, and 514 subjects were randomized to the

HLX14 group (n=256) or the EU-Prolia (n=258) group. All the randomized subjects received the first dose of study treatment. A total of 471 subjects (91.6%) completed Week 26 dose. A total of 478 subjects (93.0%) completed Week 52 visit. The most common reason for treatment discontinuation was withdrawal of informed consent followed by subject decision in both groups (Table 15).

Table 15: Patient Disposition for Study HLX14-002-PMOP301

	HLX14	EU-Prolia	Total
Randomized	256	258	514
Completed Week 26 treatment	**234 (91.4%)**	**237 (91.9%)**	**471 (91.6%)**
Discontinued treatment	22 (8.6%)	21 (8.1%)	43 (8.4%)
adverse event	0	1 (0.4%)	1 (0.2%)
Withdrawal of informed consent	10 (3.9%)	11 (4.3%)	21 (4.1%)
Lost to follow up	2 (0.8%)	0	2 (0.4%)
Poor compliance	3 (1.2%)	0	3 (0.6%)
Subject decision	7 (2.7%)	9 (3.5%)	16 (3.1%)
Completed study on Week 52	**236 (92.2%)**	**242 (93.8%)**	**478 (93.0%)**
Discontinued study	20 (7.8%)	16 (6.2%)	36 (7.0%)
Adverse event	0	1 (0.4%)	1 (0.2%)
Withdrawal of informed consent	11 (4.3%)	11 (4.3%)	22 (4.3%)
Lost to follow up	2 (0.8%)	0	2 ().4%)
Poor compliance and fails to attend	2 (0.8%)	1 (0.4%)	3 (0.6%)
Subject decision	5 (2.0%)	3 (1.2%)	8 (1.6%)

[Source: excerpted from Table 10-1 of the CSR]

Demographics and Baseline Characteristics

Based on the ITT set, the baseline demographic and baseline characteristics of subjects in the HLX14 and the Prolia groups were comparable (Table 16 and Table 17). Baseline BMD values were also comparable between the two groups (Table 18).

Table 16: Baseline Demographics

	HLX14 N=256	EU-Prolia N=258	Total N=514
Age categories (years), n (%)			
<65	81 (31.6)	83 (32.2)	164 (31.9)
≥65	175 (68.4)	175 (67.8)	350 (68.1)
Age categories (years), n (%)			
<60	17 (6.6)	19 (7.4)	36 (7.0)
60-85	237 (92.6)	238 (92.2)	475 (92.4)
>85	2 (0.8)	1 (0.4)	3 (0.6)
Age, years			
Mean (SD)	66.9 (5.9)	67.0 (5.8)	67.0 (5.8)
Median	67.0	67.0	67.0
Q1, Q3	63, 71	63.70	63, 70
Min, Max	52, 87	51, 86	51, 87
Race, n (%)			
Asian	255 (99.6)	257 (99.6)	512 (99.6)
White	1 (0.4)	1 (0.4)	2 (0.4)
Region, n (%)			
Asian	255 (99.6)	257 (99.6)	512 (99.6)
Non-Asian	1 (0.4)	1 (0.4)	2 (0.4)
Ethnicity, n (%)			
Han Chinese	251 (98.0)	251 (97.3)	502 (97.7)
Other	4 (1.6)	7 (2.7)	11 (2.1)
Not reported	1 (0.4)	0	1 (0.2)

Abbreviations: N = number of patients randomized; Q1=25th percentile; Q3=75th percentile; SD = standard deviation; cell content shows frequency and percentage relative to N in the parentheses; [Source: Statistical Reviewer Analysis; adsl.xpt]

Table 17: Baseline Characteristics

	HLX14 N=256	EU-Prolia N=258	Total N=514
BMI (kg/m^2) categories, n (%)			
<25	184 (71.9)	184 (71.3)	368 (71.6)
25-30	70 (27.3)	71 (27.5)	141 (27.4)
>30	2 (0.8)	3 (1.2)	5 (1.0)
Body weight, kg			
Mean (SD)	55.8 (7.3)	55.9 (7.7)	55.9 (7.5)

Median	56.0	56.0	56.0
Q1, Q3	50.2, 60.9	50.7, 61.3	50.5, 61.0
Min, Max	35.5, 77.5	36.0, 77.8	35.5, 77.8
BMI, kg/m^2			
Mean (SD)	23.3 (2.9)	23.4 (3.0)	23.3 (2.9)
Median	23.5	23.2	23.3
Q1, Q3	21.3, 25.3	21.3, 25.4	21.3, 25.4
Min, Max	14.2, 32.3	14.6, 31.4	14.2, 32.3
Height, cm			
Mean (SD)	154.8 (5.6)	154.8 (5.6)	154.8 (5.6)
Median	155.0	155.0	155.0
Q1, Q3	150.8, 159	150.5, 158.2	150.5, 158.5
Min, Max	137.4, 168.0	135.7, 174.5	135.7, 174.5
Prior use of bisphosphonate, n (%)			
Yes	11 (4.3)	8 (3.1)	19 (3.7)
No	245 (95.7)	250 (96.9)	495 (96.3)

Abbreviations: N = number of patients randomized; Q1=25th percentile; Q3=75th percentile; SD = standard deviation; cell content shows frequency and percentage relative to N in the parentheses; [Source: Statistical Reviewer Analysis; adsl.xpt]

Table 18: Baseline BMD by Central Imaging

	HLX14 N=256	EU-Prolia N=258	Total N=514
BMD at lumbar spine, g/cm^2			
Mean (SD)	0.74 (0.08)	0.74 (0.08)	0.74 (0.08)
Median	0.73	0.73	0.73
Q1, Q3	0.68, 0.79	0.69, 0.79	0.68, 0.79
Min, Max	0.49, 0.91	0.54, 0.92	0.49, 0.92
BMD at total hip, g/cm^2			
Mean (SD)	0.71 (0.09)	0.70 (0.09)	0.70 (0.09)
Median	0.70	0.70	0.70
Q1, Q3	0.64, 0.76	0.63, 0.77	0.64, 0.76
Min, Max	0.46, 1.01	0.47, 1.00	0.46, 1.01
BMD at femoral neck, g/cm^2			
Mean (SD)	0.61 (0.10)	0.61 (0.10)	0.61 (0.10)
Median	0.60	0.61	0.60
Q1, Q3	0.55, 0.67	0.54, 0.68	0.54, 0.67
Min, Max	0.36, 0.97	0.36, 0.93	0.36, 0.97

Abbreviations: N = number of patients randomized; Q1=25th percentile; Q3=75th percentile; SD = standard deviation;
[Source: Statistical Reviewer Analysis; adsl.xpt, adeffbmd.xpt]

Analysis of Primary Clinical Endpoint(s)

Missing data

The amount of missing data is shown in Table 19 for each treatment group. The percentage of missing data were 7.8% in the HLX14 group and 6.6% in the EU-Prolia group.

For the pre-specified primary efficacy analysis, 20 observed data from the HLX15 group and 17 observed data from the Prolia group were not included in the analyses but were imputed instead based on corresponding intercurrent events (see Statistical Methodologies of this review). Therefore, the number of imputed values for the primary analysis was 40 for the HLX14 group and 34 for the EU-Prolia group. The imputation was based on either the WOCF or the MAR, as specified in Statistical Methodologies of this review.

Table 19: Summary of Observed/Missing data

	HLX14 (N=256)	EU-Prolia(N=258)
Observed primary endpoint	236 (92.2%)	241 (93.4%)
Included In the primary analysis	216	224
Not included in the primary analysis	20	17
Missing primary endpoint	20 (7.8%)	17 (6.6%)
Number imputed for the primary analysis	40	34

Abbreviations: N=number of patients randomized; [Source: Section 11.4.1. of the CSR and Response to IR dated October 22, 2024]

Applicant's pre-specified analysis

Table 20 presents the results from the applicant's prespecified analysis. The 90% confidence interval fell within the pre-specified equivalence margins (-1.45%, 1.45%).

Table 20: Percent change from Baseline to Week 52 in LS-BMD

Statistics	HLX14 N=256	EU-Prolia N=258
Baseline mean (SD)	0.74 (0.08)	0.74 (0.08)
%Change in LS-BMD		
Estimate, LSMean (SE)[1]	5.95 (0.69)	5.72 (0.69)
Difference from Prolia	0.23	
90% CI	-0.36, 0.83	
Imputed, n(%)	40 (15.63)	34 (13.18)

Abbreviations: LS-BMD=bone mineral density at lumbar spine; N=number of subjects randomized; SD=standard deviation; LSMean=least squares mean; SE=standard error; CI=confidence interval; [1]Model based estimates and standard error, the ANCOVA model included treatment and stratification group as factors and baseline value as a covariate; Missing values were imputed using either WOCF or multiple imputation based on the MAR according to the types of ICEs; 200 imputed datasets were generated;
Source: Statistical Reviewer Analysis; adsl.xpt, adeffbmd.xpt

Applicant's additional analysis in the Response to the IR letter

The analysis results are shown in Table 21 and Table 22. In this analysis, the applicant imputed missing measurements assuming missing at random for each treatment group before shifting the imputed values in the HLX14 group by the margin. Note that this imputation approach is not the FDA's preferred imputation under the corresponding null approach.

Table 21: Percent change from Baseline to Week 52 in LS-BMD: Non-inferior Test

Statistics	HLX14 N=256	EU-Prolia N=258
Baseline mean (SD)	0.74 (0.08)	0.74 (0.08)
%Change in LS-BMD		
Estimate, LSMean (SE)[1]	5.75 (0.69)	5.80 (0.69)
Difference from Prolia	-0.05	
90% CI	-0.65, 0.55	
Imputed, n(%)	40 (15.63)	34 (13.18)

Abbreviations: LS-BMD=bone mineral density at lumbar spine; N=number of subjects randomized; SD=standard deviation; LSMean=least squares mean; SE=standard error; CI=confidence interval; [1]Model based estimates and standard error, the ANCOVA model included treatment and stratification group as factors and baseline value as a covariate; Missing values were imputed based on the MAR and imputed values for the HLX group were worsen by a non-inferiority margin 1.45%; 200 imputed datasets were generated; [Source: Statistical Reviewer Analysis; adsl.xpt, adeffbmd.xpt]

Table 22: Percent change from Baseline to Week 52 in LS-BMD: Non-superior Test

Statistics	HLX14 N=256	EU-Prolia N=258
Baseline mean (SD)	0.74 (0.08)	0.74 (0.08)
%Change in LS-BMD		
Estimate, LSMean (SE)[1]	6.14 (0.69)	5.74 (0.69)
Difference from Prolia	0.40	
90% CI	-0.20, 1.00	
Imputed, n(%)	40 (15.63)	34 (13.18)

Abbreviations: LS-BMD=bone mineral density at lumbar spine; N=number of subjects randomized; SD=standard deviation; LSMean=least squares mean; SE=standard error; CI=confidence interval; [1]Model based estimates and standard error, the ANCOVA model included treatment and stratification group as factors and baseline value as a covariate; Missing values were imputed based on the MAR and imputed values for the HLX group were increased by a non-superiority margin 1.45%; 200 imputed datasets were generated; [Source: Statistical Reviewer Analysis; adsl.xpt, adeffbmd.xpt]

The 90% confidence intervals obtained from both one-sided tests fell within the pre-specified equivalence margins (-1.45%, 1.45%), demonstrating the similarity between HLX14 and EU-Prolia. The conclusion on the biosimilarity remains unchanged from the Applicant's pre-specified primary analysis.

Based on FDA preferred imputation under the null approach

Statistical reviewer has performed additional analysis implementing preferred imputation under the null approach. Missing Week 52 measurements in the HLX14 were imputed based on baseline data and the observed Week 52 measurements from the EU-Prolia group. Missing Week 52 measurement in the Prolia group were imputed based on the

observed measurements based on MAR. The imputed values of the HLX14 group were then subtracted by the margin 1.45% for testing non-inferiority and added by the margin 1.45% for testing non-superiority. The results are shown in Table 23 and Table 24. The conclusion on the biosimilarity remains unchanged from the Applicant's prespecified analysis.

Table 23: Percent change from Baseline to Week 52 in LS-BMD: Non-inferior Test

Statistics	HLX14 N=256	EU-Prolia N=258
Baseline mean (SD)	0.74 (0.08)	0.74 (0.08)
%Change in LS-BMD		
Estimate, LSMean (SE)[1]	5.75 (0.70)	5.83 (0.70)
Difference from Prolia	-0.07	
90% CI	-0.69, 0.55	
Imputed, n(%)	40 (15.63)	34 (13.18)

Abbreviations: LS-BMD=bone mineral density at lumbar spine; N=number of subjects randomized; SD=standard deviation; LSMean=least squares mean; SE=standard error; CI=confidence interval; [1]Model based estimates and standard error, the ANCOVA model included treatment and stratification group as factors and baseline value as a covariate; Missing values were imputed based on the observed data of the Prolia group and imputed values for the HLX group were worsen by a non-inferiority margin 1.45%; 100 imputed datasets were generated;
[Source: Statistical Reviewer Analysis; adsl.xpt, adeffbmd.xpt]

Table 24: Percent change from Baseline to Week 52 in LS-BMD: Non-superior Test

Statistics	HLX14 N=256	EU-Prolia N=258
Baseline mean (SD)	0.74 (0.08)	0.74 (0.08)
%Change in LS-BMD		
Estimate, LSMean (SE)[1]	6.14 (0.70)	5.76 (0.70)
Difference from Prolia	0.38	
90% CI	-0.24, 1.00	
Imputed, n(%)	40 (15.63)	34 (13.18)

Abbreviations: LS-BMD=bone mineral density at lumbar spine; N=number of subjects randomized; SD=standard deviation; LSMean=least squares mean; SE=standard error; CI=confidence interval; [1]Model based estimates and standard error, the ANCOVA model included treatment and stratification group as factors and baseline value as a covariate; Missing values were imputed based on observed data of the Prolia group and imputed values for the HLX group were increased by a non-superiority margin 1.45%;; 100 imputed datasets were generated;
[Source: Statistical Reviewer Analysis; adsl.xpt, adeffbmd.xpt]

<u>Based on imputation limited to only missing Week 52 data regardless of ICEs</u>

In the Applicant's prespecified analyses, some observed Week 52 measurements were considered missing and imputed based on the prespecified ICE categories. Additional analysis was performed to impute only unobserved Week 52 measurements. Table 25

and Table 26 present results when only missing Week 52 measurements were imputed regardless of ICEs. Note that the number of imputed data are down to 20 in the HLX14 group and 17 in the EU-Prolia group. Missing data were multiply imputed under the correspond null. The conclusion on the biosimilarity remains unchanged.

Table 25: Percent change from Baseline to Week 52 in LS-BMD: Non-inferior Test

Statistics	HLX14 N=256	EU-Prolia N=258
Baseline mean (SD)	0.74 (0.08)	0.74 (0.08)
%Change in LS-BMD		
Estimate, LSMean (SE)[1]	5.65 (0.64)	5.67 (0.63)
Difference from Prolia	-0.03	
90% CI	-0.62, 0.57	
Imputed, n(%)	20 (7.8%)	17 (6.6%)

Abbreviations: LS-BMD=bone mineral density at lumbar spine; N=number of subjects randomized; SD=standard deviation; LSMean=least squares mean; SE=standard error; CI=confidence interval; [1]Model based estimates and standard error, the ANCOVA model included treatment and stratification group as factors and baseline value as a covariate; Missing values were imputed based on the observed data of the Prolia group and imputed values for the HLX group were worsen by a non-inferiority margin 1.45%; 100 imputed datasets were generated;
[Source: Statistical Reviewer Analysis; adsl.xpt, adeffbmd.xpt]

Table 26: Percent change from Baseline to Week 52 in LS-BMD: Non-superior Test

Statistics	HLX14 N=256	EU-Prolia N=258
Baseline mean (SD)	0.74 (0.08)	0.74 (0.08)
%Change in LS-BMD		
Estimate, LSMean (SE)[1]	5.85 (0.64)	5.65 (0.63)
Difference from Prolia	0.20	
90% CI	-0.39, 0.80	
Imputed, n(%)	20 (7.8%)	17 (6.6%)

Abbreviations: LS-BMD=bone mineral density at lumbar spine; N=number of subjects randomized; SD=standard deviation; LSMean=least squares mean; SE=standard error; CI=confidence interval; [1]Model based estimates and standard error, the ANCOVA model included treatment and stratification group as factors and baseline value as a covariate; Missing values were imputed based on the observed data of the EU-Prolia and imputed values for the HLX group were increased by a non-superiority margin 1.45%; 100 imputed datasets were generated;
[Source: Statistical Reviewer Analysis; adsl.xpt, adeffbmd.xpt]

Additional sensitivity analyses were conducted to assess the robustness of the primary results under various approaches to handle missing values including a tipping point analysis. All results supported the similarity conclusion.

Results from Subgroup analysis

The Applicant presented subgroup results in the submission (Table 14.2.1.3.2 of efficacy-pk-and-immunogenicity-tables.pdf). The results from various subgroups did not reveal any concerning findings. Note that these analyses are considered as exploratory. Subgroup analyses by geographical region, race, ethnicity, and sex were not performed due to the majority was Chinese in Asian and all of them were females. Subgroup analysis for age <65 and age ≥65 is summarized in Table 27.

Table 27: Subgroup analysis of Percent change from Baseline to Week 52 in LS-BMD

		HLX14 (N=256)	EU-Prolia (N=258)
Age <65	n	81	83
	Mean (SD)	0.74 (0.08)	0.74 (0.08)
	LSMean (SE)[1]	6.10 (0.44)	5.45 (0.43)
	Diff (95% CI)	0.65 (-0.58, 1.87)	
Age ≥65	n	175	175
	Mean (SD)	0.73 (0.08)	0.74 (0.08)
	LSMean (SE)[1]	5.81 (0.31)	6.04 (0.31)
	Diff (95% CI)	-0.23 (-1.10, 0.64)	

Abbreviations: LS-BMD=bone mineral density at lumbar spine; N=number of subjects randomized; n=number of subjects in the subgroup; SD=standard deviation; LSMean=least squares mean; SE=standard error; Diff= difference from EU-Prolia; CI=confidence interval; [1]Model based estimates and standard error, mixed model for repeated measures (MMRM), with treatment, stratification factor, visit, and treatment by visit interaction as factors, and the respective baseline BMD as covariate, an unstructured covariance matrix used to model the covariance structure; Treatment policy is applied for all intercurrent events (ICEs). All data collected after ICEs is used; [source: Excerpted from Table 14.2.1.3.2 of efficacy-pk-and-immunogenicity-tables.pdf]

6.3. Review of Safety Data

6.3.1. Methods

Clinical Studies Used to Evaluate Safety

Two clinical studies were reviewed to evaluate safety as listed in Section 2.2. The PK Similarity Study (HLX14-001) and the Comparative Clinical Study (HLX14-002-PMOP301, hereafter referred to as 002-PMOP301). Study HLX14-001 is described in Table 2. The results of the safety review for Study HLX14-001 are summarized in Table 47 and discussed in the Additional Safety Evaluations section.

Study 002-PMOP301 was a randomized, double-blind, parallel controlled comparative clinical study to compare HLX14 to EU-Prolia in postmenopausal women with osteoporosis at high risk for fracture. This study consisted of two treatment periods: The Main Period (from Week 1 to week 52) which consisted of 256 patients who received HLX14 60 mg vial subcutaneous injection every six months and 258 patients who received EU-Prolia 60 mg PFS subcutaneous injection every six months. The Extension

Period (from Week 52 to Week 78) was a single transition period in which 220 patients assigned to EU-Prolia were re-randomized to receive a third dose of either EU-Prolia (110 patients) or HLX14 (110 patients).

The safety population was defined as consisting of all subjects who received at least one Investigational Product (IP) administration during the study period. Safety data were not combined because the study populations and designs differed in Study HLX14-001 and Study 002-PMOP301. The safety database from the perspective of a demonstration of no clinically meaningful differences is considered acceptable in terms of size and adequacy.

Categorization of Adverse Events

All adverse events (AEs) for Study HLX14-001 were coded using MedDRA Version 26.1 and for Study 002-PMOP301 were coded using MedDRA Version 27.0. For both studies an adverse event was defined as:

Any untoward medical occurrence in a patient or a clinical investigation of subjects taking a drug that was not necessarily casually related to the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, regardless of the relationship with the medicinal product.

An AE during the clinical trial that met any one of the following criteria was considered a Serious Adverse Event (SAE):

- Leading to death.
- Life-threatening (NOTE: the term “life-threatening” in the definition of “serious” referred to an event in which the subject was at risk of death at the time of the event; it did not refer to an event which hypothetically might cause death if it were more severe).
- Requiring inpatient hospitalization or prolongation of existing hospitalization (if a subject experienced pre-existing discomfort or a disease prior to the enrollment in the study and was scheduled for hospitalization and/or surgery before the start of the study or during the study, but the situation did not worsen unexpectedly during the study, it was not deemed as a SAE.
- Leading to persistent or significant disability/incapacity.
- Leading to congenital anomaly/birth defect.
- Other important medical events: (it might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events were intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that did not result in hospitalization; or development of drug dependency or drug abuse).

AEs were graded by the Investigator based on the National Cancer Institute (NCI) – common terminology criteria for adverse events (CTCAE) V5.0 for both studies.

The Applicant's approach for recording, coding, and categorizing AEs, as well as their approach to safety analyses was reasonable and appropriate. In some analyses, the reviewer used the definition of a treatment emergent adverse event (TEAE) defined as any event not present before exposure to study drug or worsening of an existing event after exposure to study drug.

Safety Analyses

Safety data were not combined because the study populations and designs differed for Study HLX14-001 and Study 002-PMOP301. Study 002-PMOP301 consisted of two treatment periods – the first (Main Period) compared HLX14 and EU-Prolia and the second (Extension Period) examining the safety of a transition from EU-Prolia to HLX14 compared to continuing on EU-Prolia. Safety data from the two treatment periods are presented separately. The specific analyses performed on the safety data are described in the relevant sections of this review.

6.3.2. Major Safety Results

The safety overview according to treatment received at the time of any adverse event and by the treatment sequence is presented in Table 28. Patients were included in the safety set if they received at least one dose of HLX14 or EU-Prolia. The safety analysis set consists of all treated patients, with treatment assignment based on actual treatment received. There were 256 patients who received HLX14 and 258 patients who received EU-Prolia in the Main Period. For the Extension Period, 110 patients who received EU-Prolia were switched to HLX14 and 110 patients who received EU-Prolia remained on EU-Prolia. A third arm consisting of 220 patients who received HLX14 remained on HLX14.

The number of patients experiencing one or more adverse events was comparable across all treatments within the Main Period and the Extension Period. There were no reported deaths during the study. Adverse Events equal to or greater than a grading of Grade 3 were generally well-balanced between the two treatments. Further details are provided in the relevant sections of the review.

Table 28: Safety Overview of Study 002-PMOP301

Patients[a] experiencing ≥1:	Main Period		Extension Period		
	HLX14 N=256 n (%)	EU-Prolia N=258 n (%)	EU-Prolia/ HLX14 N=110 n (%)	EU-Prolia/ EU Prolia N=110 n (%)	HLX14/ HLX14 N=220 n (%)
Adverse Events Grades 1 to 5 Grades 3 to 5	222 (86.7) 25 (9.8)	230 (89.1) 19 (7.4)	64 (58.2) 1 (0.9)	57 (51.8) 6 (5.4)	108 (49.1) 6 (2.8)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious Adverse Events	23 (9.0)	16 (6.2)	0 (0)	0 (0)	1 (0.5)
Discontinuations due to AE	0 (0)	3(1.2)	0 (0)	0 (0)	0 (0)

[a]For each category, patients are included only once, even if they experienced multiple events in the same category.
Source: Reviewer's table, AE, ADAE datasets. OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: SAFFL = 'Y'; Column Variable 1: PHASE; Column Variable 2: TRTNEW. Any AE - Dataset: Adverse Events.

Relevant Characteristics of the Population Evaluated for Safety

The patient demographics and baseline characteristics of the safety population for Study 002-PMOP301 are described in Table 29. The study treatments were balanced in terms of study population demographics and baseline characteristics.

Table 29: Study 002-PMOP301 demographics and baseline characteristics (Safety Population)

	HLX14 N=256	EU-Prolia N=258
Age (years)		
Mean (SD)	66.9 (5.89)	67.0 (5.80)
Median (Min, Max)	67.0 (52, 87)	67.0 (51, 86)
Age Category n (%)		
< 60	17 (6.6)	19 (7.4)
60-85	237 (92.6)	238 (92.2)
>85	2 (0.8)	1 (0.4)
<65	81 (31.6)	83 (32.2)
≥65	175 (68.4)	175 (67.8)
Sex n (%)		
Female	256 (100)	258 (100)
Race n (%)		
Asian	255 (99.6)	257 (99.6)
White	1 (0.4)	1 (0.4)
Prior Bisphosphonate use n (%)		
Yes	11 (4.3)	8 (3.1)
No	245 (95.7)	250 (96.9)
History of hip fracture n (%)		
Yes	16 (6.3)	23 (8.9)
No)	240 (93.8)	235 (91.1)

Source: Reviewer's table. OCS Analysis Studio, Custom Tool. Dataset: DM

Exposure

The exposure to investigational products for patients in Study 002-PMOP301 is summarized in Table 30. Exposure to study drug was similar across treatments arms. All patients received at least one 60 mg dose of HLX14 or EU-Prolia. During the Main Period of the study, 22 (8.6%) patients received only the first 60 mg dose of HLX14 and 21 (8.1%) of patients received the first 60 mg dose of EU-Prolia. For the second dose, 234 (91.4%) of patients received the second 60 mg dose of HLX14 and 237 (91.9%) of patients received the second 60 mg dose of EU-Prolia. All patients that continued onto the Extension Period received a third dose of either HLX14 or EU-Prolia (Table 31).

Table 30: Exposure of Study Drug during Main Period

60 mg doses received	HLX14 N=256 n (%)	EU-Prolia N=258 n (%)
1	22 (8.6)	21 (8.1)
2	234 (91.4)	237 (91.9)

Source: Reviewer's table EX dataset, CSR p8

Table 31: Exposure of Study Drug during Extension Period

60 mg doses received	EU-Prolia/HLX14 N=110 n (%)	EU-Prolia/EU-Prolia N=110 n (%)	HLX14/HLX14 N=220 n (%)
1	110 (100)	110 (100)	220 (100)

Source: Reviewer's Table, EX dataset

Deaths

There were no reported deaths on Study 002-PMOP301.

Serious Adverse Events

During the Main Period of Study 002-PMOP301, 23 (9%) of patients on the HLX14 arm experienced one or more SAEs and 16 (6.2%) of patient on the EU-Prolia arm experienced one or more SAEs (Table 32). While the overall number of SAEs were high, the occurrences were balanced between arms. All patient narratives were evaluated, and none of the SAEs were determined to be related to study drug. Narratives from patients who experienced an SAE of Femoral neck fracture, Thoracic vertebrae facture, Lumbar vertebrae fracture, and Pneumonia follow.

Summary Narratives for the patients with SAE of Femoral neck fracture, Thoracic vertebrae facture, Lumbar vertebrae fracture, and Pneumonia during the Main Period:

- Patient (b) (6) a 69-year-old female receiving HLX14 fell while riding a bicycle and injured her left hip 9 days after receiving the study drug. She was admitted to the hospital the same day and diagnosed with a Femoral neck fracture (reported term: fracture of left femoral neck). She received hip arthroplasty and myoplasty for treatment of femoral neck fracture 2 days later. She fully recovered after four months and completed the study. This event was likely secondary to the fall, and unlikely to be related to study drug.
- Patient (b) (6) a 67-year-old female three days after receiving study drug (HLX14), had an MRI and hydrography of thoracic vertebra for unknown presentation which showed flattening of the T12 vertebra and edema of the bone marrow. The patient was hospitalized and diagnosed with thoracic vertebral fracture (reported term: fracture of the T12 thoracic vertebra). She had percutaneous puncture vertebroplasty, and symptomatic treatment was given after surgery with a full recovery. She completed the study with no other issues. This event was unlikely to be related to the drug.
- Patient (b) (6) a 66-year-old female receiving EU-Prolia was diagnosed with lumbar vertebral fracture by MRI 209 days after receiving the study drug. She initially reported lumbar pain 1 month before due to a traffic accident leading to the diagnosis. She underwent percutaneous vertebroplasty surgery and recovered. She received the Week 52 dose of study medication. She was also diagnosed with obstructive airway disorder approximately 1 month after receiving the study drug and was treated at the hospital. She fully recovered and completed the study. This event was likely due to lack of osteoporosis

improvement (L-spine t-score was -3.5 at baseline and -3.4 at Week 52).

- Patient (b) (6), a 59-year-old female who was receiving EU-Prolia presented with generalized fatigue and lack of appetite 186 days after receiving the study drug. She was seen at a hospital where a CT scan showed multilocular bronchiectasis of both lungs, mucus plugs in trachea and bilateral bronchi, chronic bronchitis, and emphysema. She was diagnosed with pneumonia and septic shock and treated with antibiotics. She completed the study with no other issues. Four hundred sixty-eight days after receiving study drug, she experienced sudden onset of chest pain. A CT scan showed emphysema, thickening of tube wall and mucous thrombus in lumen more predominant in right lower lobe. She was admitted to the hospital, treated with antibiotics. She fully recovered. Due to lack of temporal association, these events were likely not due to study drug.

Table 32: Study 002-PMOP301 Main Period Summary of Serious Adverse Events by SOC and PT

System Organ Class Preferred Term	**HLX14** **N = 256** **n (%)**	**EU-Prolia** **N = 258** **n (%)**
Patients[a] experiencing ≥1:	23 (9.0)	16 (6.2)
Injury, poisoning and procedural complications	**6 (2.3)**	**4 (1.6)**
Humerus fracture	2 (0.8)	0 (0.0)
Concussion	1 (0.4)	0 (0.0)
Femoral neck fracture	1 (0.4)	0 (0.0)
Meniscus injury	1 (0.4)	0 (0.0)
Thoracic vertebral fracture	1 (0.4)	0 (0.0)
Lumbar vertebral fracture	0 (0.0)	1 (0.4)
Patella fracture	0 (0.0)	1 (0.4)
Spinal compression fracture	0 (0.0)	1 (0.4)
Toxicity to various agents	0 (0.0)	1 (0.4)
Nervous system disorders	**4 (1.6)**	**2 (0.8)**
Cerebral hypoperfusion	1 (0.4)	0 (0.0)
Cerebral infarction	1 (0.4)	1 (0.4)
Intracranial aneurysm	1 (0.4)	0 (0.0)
Lacunar infarction	1 (0.4)	0 (0.0)
Transient ischemic attack	1 (0.4)	1 (0.4)
Infections and infestations	**3 (1.2)**	**2 (0.8)**
Appendicitis	1 (0.4)	1 (0.4)
Complicated appendicitis	1 (0.4)	0 (0.0)
Gastroenteritis	1 (0.4)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.4)

System Organ Class Preferred Term	HLX14 N = 256 n (%)	EU-Prolia N = 258 n (%)
Patients[a] experiencing ≥1:	23 (9.0)	16 (6.2)
Septic shock	0 (0.0)	1 (0.4)
Musculoskeletal and connective tissue disorders	**3 (1.2)**	**3 (1.2)**
Lumbar spinal stenosis	1 (0.4)	0 (0.0)
Rotator cuff syndrome	1 (0.4)	1 (0.4)
Spinal osteoarthritis	1 (0.4)	0 (0.0)
Intervertebral disc protrusion	0 (0.0)	1 (0.4)
Synovitis	0 (0.0)	1 (0.4)
Ear and labyrinth disorders	**2 (0.8)**	**1 (0.4)**
Meniere's disease	1 (0.4)	0 (0.0)
Vertigo positional	1 (0.4)	0 (0.0)
Otolithiasis	0 (0.0)	1 (0.4)
Eye disorders	**2 (0.8)**	**0 (0.0)**
Cataract	1 (0.4)	0 (0.0)
Neovascular age-related macular degeneration	1 (0.4)	0 (0.0)
Gastrointestinal disorders	**2 (0.8)**	**3 (1.2)**
Colitis	1 (0.4)	0 (0.0)
Large intestine polyp	1 (0.4)	0 (0.0)
Gastritis	0 (0.0)	1 (0.4)
Hemorrhoids	0 (0.0)	2 (0.8)
Cardiac disorders	**1 (0.4)**	**1 (0.4)**
Coronary artery disease	1 (0.4)	1 (0.4)
Renal and urinary disorders	**1 (0.4)**	**0 (0.0)**
Ureterolithiasis	1 (0.4)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0.0)**	**1 (0.4)**
Cervix carcinoma	0 (0.0)	1 (0.4)
Reproductive system and breast disorders	**0 (0.0)**	**1 (0.4)**
Uterine polyp	0 (0.0)	1 (0.4)

[a]For each category, patients are included only once, even if they experienced multiple events in the same category.
Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "HLX14" and SAFFL = "Y" (HLX14); TRT01A = "Prolia" and SAFFL = "Y" (Prolia); TRTEMFL = "Y" and TRT1EMFL = "Y" and AESER = "Y" (Adverse Events), Case Report Narratives

During the Extension Period of Study 002-PMOP301, 1 patient in each arm experienced one SAE (Table 33). These were all coded with the PT of Spinal compression fracture. All patient narratives were evaluated, and none of the SAEs were determined to be

related to study drug. Narratives from these patients follow.

Summary Narratives for the patients with SAE of Spinal compression fracture during the Extension Period:

- Patient (b) (6) a 73-year-old female receiving HLX14 was admitted to the hospital two days after receiving the study drug for a lumbar vertebral compression fracture following a fall. The lumbar plain scan with three-dimensional reconstruction showed lumber vertebral compression fracture. The subject was diagnosed with spinal compression fracture (reported term: lumbar 1 vertebral body compression fracture). She underwent vertebroplasty and recovered. She completed the study with no other issues. This event was unlikely to be related to the drug.
- Patient (b) (6) a 68-year-old female receiving HLX14 who fell at home 382 days after receiving the study drug. She went to an orthopedic surgeon two days later and an MRI showed possible T12 vertebral compression fracture. She was also diagnosed with spinal compression fracture with reported term: compression fractures of lumbar spine. She underwent a T12 percutaneous vertebral balloon dilation and discharged with pain meds and fully recovered. This event was likely related to the fall. Earlier in the study, she presented with left knee pain after receiving Week 26 of study drug. She was admitted to the hospital where an MRI showed a tear in the meniscus of the medial side of left knee joint and degeneration of the posterior lateral meniscus. She underwent arthroscopic partial meniscus resection of the left knee with debridement. She recovered from the surgery and continued the study. She was also diagnosed with cervical radiculopathy and had surgery 358 days after receiving the study drug.
- Patient (b) (6) a 62-year-old female receiving EU-Prolia who fell 523 days after receiving study drug resulting in lower back pain and limited movement. She went to the hospital where MRI showed T12 compression fracture of thoracic vertebra. CT showed T12 vertebral compression fracture, degenerative changes in the T11-L1. She underwent percutaneous taperplasty and fully recovered. She completed the study with no other complications. L-spine t-score improved from -2.69 at baseline to -2.16 at 52-weeks. The reported event may have been due to the fall. Earlier in the study, she experienced right lower abdominal pain 54 days after receiving the study drug. She went to the hospital where a CT scan showed acute appendicitis with fecal stone. A laparoscopic appendectomy was performed. She recovered and continued the study.

Table 33: Study 002-PMOP301 Extension Period Summary of Serious Adverse Events by SOC and PT

Patients[a] experiencing ≥1:			
System Organ Class Preferred Term	**HLX14/ EU-Prolia N=110 n (%)**	**EU-Prolia/ EU-Prolia N=110 n (%)**	**HLX14/ HLX14 N=220 n (%)**

Patients[a] experiencing ≥1:			
Injury, poisoning and procedural complications Spinal compression fracture	**1 (0.9)** 1 (0.9)	**1 (0.9)** 1 (0.9)	**1 (0.5)** 1 (0.5)

[a]For each category, patients are included only once, even if they experienced multiple events in the same category.
Source: Reviewer's Table, AE, ADAE datasets, Case Report Narratives

Treatment Emergent Adverse Events

Treatment Emergent Adverse Events experienced in greater than or equal to 2% of patients are displayed by SOC and PT for the Main Period in Table 34. The greatest number of treatment emergent adverse events was in the System Organ Class (SOC) for Metabolism and Nutrition disorders. This was driven by the number of patients with Hyperlipidemia and Vitamin D deficiency. The incidences were similar between arms in the both the Main Period and the Extension Period (Table 34 and Table 35). With the exception of one patient in the Main Period who had Hyperlipidemia Grade 3 (Table 34), all other patients with Hyperlipidemia and Vitamin D deficiency were Grade 1 or Grade 2 in severity with the majority Grade 1. There was a discrepancy in the number of patients in the Main Period with a TEAE of Vitamin D deficiency and TEAE of Vitamin D decreased. While balanced between arms (Main Period Vitamin D deficiency HLX14 34 (13.3%), EU-Prolia 42 (16.3%) and (Main Period Vitamin D decreased HLX14 1 (0.4%), EU-Prolia 2 (0.8%), the higher levels of patients with Vitamin D deficiency versus Vitamin D decreased are likely due to investigator judgement as to which safety event term to assign to the adverse event. The protocol did not pre-specify a distinction between Vitamin D deficiency and Vitamin D decreased and both terms were likely used to capture the same observation.

Table 34: Treatment Emergent Adverse Events occurring in ≥2% of patients for each treatment by MedDRA System Organ Class and Preferred Term (Main Period)

Patients[a] experiencing ≥1:	Main Period	
System Organ Class Preferred Term	**HLX14** **N=256** **n (%)**	**EU-Prolia** **N=258** **n (%)**
Metabolism and nutrition disorders	**110 (43.0)**	**117 (45.3)**
Hyperlipidemia	39 (15.2)	45 (17.3)
Vitamin D deficiency	34 (13.3)	42 (16.3)
Hyperuricemia	17 (6.6)	15 (5.8)
Hypercalcemia	9 (3.5)	14 (5.4)
Hyperglycemia	8 (3.2)	4 (1.6)
Hypocalcemia	7 (2.7)	13 (5.0)
Hypertriglyceridemia	6 (2.3)	4 (1.6)
Dyslipidemia	5 (2.0)	2 (0.0)
Hypochloremia	5 (2.0)	5 (1.9)
Hypokalemia	5 (2.0)	5 (1.9)
Hypophosphatemia	5 (2.0)	8 (3.1)
Investigations	**94 (36.7)**	**105 (40.7)**
Urinary occult blood positive	14 (5.5)	14 (5.4)
Weight decreased	11 (4.3)	15 (5.8)
ALT increased	10 (3.9)	8 (3.1)
Blood glucose increased	10 (3.9)	7 (2.7)
White blood cells urine positive	10 (3.9)	9 (3.5)
ECG T wave abnormal	9 (3.5)	14 (5.4)
Fibrin dimer increased	9 (3.5)	8 (3.1)
Weight increased	8 (3.1)	4 (1.6)
AST increased	7 (2.7)	5 (1.9)
Blood alkaline phosphatase increased	7 (2.7)	3 (1.2)
Blood creatinine increased	7 (2.7)	2 (0.8)
White blood cell count decreased	7 (2.7)	3 (1.2)
ECG ST- segment abnormal	5 (2.0)	3 (1.2)
Infection and infestations	**89 (34.8)**	**88 (34.1)**
Urinary tract infections	32 (12.5)	38 (14.7)
Upper respiratory tract infection	20 (7.8)	22 (8.5)
Covid-19	15 (5.9)	19 (7.4)
Asymptomatic bacteriuria	6 (2.3)	3 (1.2)
Pneumonia	6 (2.3)	3 (.2)
Pharyngitis	5 (2.0)	2 (0.8)
General disorders and administration site conditions	**63 (24.6)**	**74 (28.7)**
Pyrexia	50 (19.5)	58 (22.5)
Pain	5 (2.0)	4 (1.6)

Patients[a] experiencing ≥1:	Main Period	
System Organ Class Preferred Term	**HLX14** **N=256** **n (%)**	**EU-Prolia** **N=258** **n (%)**
Respiratory, thoracic and mediastinal disorders	**63 (24.6)**	**73 (28.3)**
Cough	49 (19.1)	53 (20.5)
Oropharyngeal pain	10 (3.9)	18 (7.0)
Musculoskeletal and connective tissue disorders	**59 (23.0**	**52 (20.2)**
Arthralgia	14 (5.5)	8 (3.1)
Osteoarthritis	11 (4.3)	8(3.1)
Back pain	10 (3.9)	3 (1.2)
Spinal osteoarthritis	10 (3.9)	10 (3.9)
Myalgia	6 (2.3)	4 (1.6)
Spondylolisthesis	6 (2.3)	8 (3.1)
Cardiac disorders	**44 (17.2)**	**43 (16.7)**
Sinus bradycardia	11 (4.3)	3 (1.2)
Supraventricular extrasystoles	9 (3.5)	11 (4.3)
Ventricular extrasystoles	8 (3.1)	5 (1.9)
Gastrointestinal disorders	**34 (13.1)**	**43 (16.7)**
Chronic gastritis	5 (2.0)	4 (1.6)
Abdominal pain upper	4 (1.6)	1 (0.4)
Constipation	4 (1.6)	6 (2.3)
Diarrhea	2 (0.8)	7 (2.7)
Nervous system disorders	**33 (12.9)**	**35 (13.6)**
Headache	14 (5.5)	15 (5.8)
Dizziness	12 (4.7)	14 (5.4)
Blood and lymphatic system disorders	**15 (5.9)**	**12 (4.7)**
Anemia	8 (3.1)	6 (2.3)
Leukopenia	6 (2.3)	4 (1.6)
Injury, poisoning and procedural complications	**15 (5.9)**	**16 (6.2)**
Spinal compression fracture	3 (1.2)	6 (2.3)
Renal and urinary disorders	**15 (5.9)**	**7 (2.7)**
Psychiatric disorders	**11 (4.3)**	**14 (5.4)**
Insomnia	7 (2.7)	10 (3.9)
Vascular disorders	**10 (3.9)**	**7 (2.7)**
Eye disorders	**9 (3.5)**	**14 (5.4)**
Ear and labyrinth disorders	**6 (2.3)**	**5 (1.9)**

[a]For each category, patients are included only once, even if they experienced multiple events in the same category

Source: Reviewer's Table, OCS Analysis Studio, Safety Explorer. Filters: TRT01A = "HLX14" and SAFFL = "Y" (HLX14); TRT01A = "Prolia" and SAFFL = "Y" (Prolia); TRTEMFL = "Y" and TRT1EMFL = "Y" (Adverse Events)

Table 35: Treatment Emergent Adverse Events occurring in ≥2% of patients for each treatment by MedDRA System Organ Class and Preferred Term (Extension Period)

Patients[a] experiencing ≥1:			
System Organ Class Preferred Term	**HLX14/ EU-Prolia N=110 n (%)**	**EU-Prolia/ EU-Prolia N=110 n (%)**	**HLX14/ HLX14 N=220 n (%)**
Metabolism and nutrition disorders	**38 (34.5)**	35 (31.8)	**62 (28.2)**
Hyperlipidaemia	9 (8.2)	10 (9.1)	22 (10.0)
Vitamin D deficiency	17 (15.5)	9 (8.2)	17 (7.7)
Hyperuricaemia	3 (2.7)	12 (10.9)	9 (4.1)
Hypercalcaemia	5 (4.5)	3 (2.7)	7 (3.2)
Hyperglycaemia	2 (1.8)	1 (0.9)	6 (2.7)
Hypercholesterolaemia	4 (3.6)	1 (0.9)	5 (2.3)
Hypertriglyceridaemia	2 (1.8)	0 (0.0)	5 (2.3)
Hypochloraemia	2 (1.8)	3 (2.7)	5 (2.3)
Investigations	**39 (35.5)**	**34 (30.9)**	**56 (25.5)**
White blood cells urine positive	3 (2.7)	1 (0.9)	10 (4.5)
Electrocardiogram T wave abnormal	1 (0.9)	2 (1.8)	7 (3.2)
AST increased	2 (1.8)	1 (0.9)	6 (2.7)
ALT increased	2 (1.8)	2 (1.8)	5 (2.3)
Urinary occult blood positive	4 (3.6)	6 (5.5)	5 (2.3)
Blood glucose increased	2 (1.8)	3 (2.7)	4 (1.8)
Musculo/connective tissue	**19 (17.3)**	**16 (14.5)**	**34 (15.5)**
Spinal osteoarthritis	6 (5.5)	3 (2.7)	8 (3.6)
Spondylolisthesis	7 (6.4)	5 (4.5)	7 (3.2)
Bone hypertrophy	0 (0.0)	1 (0.9)	5 (2.3)
Intervertebral disc disorder	4 (3.6)	1 (0.9)	5 (2.3)
Infections and infestations	**20 (18.2)**	**21 (19.1)**	**30 (13.6)**
Urinary tract infection	1 (9.1)	9 (8.2)	13 (5.9)
Upper respiratory tract infection	3 (2.7)	7 (6.4)	9 (4.1)
Cardiac disorders	**12 (10.9)**	**13 (11.8)**	**24 (10.9)**
Sinus bradycardia	2 (1.8)	4 (3.6)	10 (4.5)
Myocardial ischaemia	1 (0.9)	1 (0.9)	5 (2.3)
Ventricular extrasystoles	3 (2.7)	3 (2.7)	4 (1.8)
Gastrointestinal disorders	**4 (3.6)**	**6 (5.5)**	**14 (6.4)**
Blood/lymphatic system disorders	**7 (6.4)**	**1 (0.9)**	**12 (5.5)**
Injury, poisoning and procedural	**6 (5.5)**	**4 (3.6)**	**12 (5.5)**
Spinal compression fracture	4 (3.6)	2 (1.8)	5 (2.3)
General/administration site	**3 (2.7)**	**3 (2.7)**	**7 (3.2)**
Nervous system disorders	**2 (1.8)**	**4 (3.6)**	**5 (2.3)**
Respiratory/thoracic/mediastinal	**2 (1.8)**	**6 (5.5)**	**5 (2.3)**
Cough	2 (1.8)	1 (0.9)	5 (2.3)

Patients[a] experiencing ≥1:			
System Organ Class Preferred Term	**HLX14/ EU-Prolia N=110 n (%)**	**EU-Prolia/ EU-Prolia N=110 n (%)**	**HLX14/ HLX14 N=220 n (%)**
Skin/subcutaneous tissue	**3 (2.7)**	**0 (0.0)**	**5 (2.3)**

[a]For each category, patients are included only once, even if they experienced multiple events in the same category
Source: Reviewer's Table, OCS Analysis Studio, Safety Explorer. Filters: TRTSEQA = "HLX14 - HLX14" and SAFETFL = "Y" (HLX14/HLX14); TRTSEQA = "Prolia - HLX14" and SAFETFL = "Y" (Prolia/HLX14); TRTSEQA = "Prolia - Prolia" and SAFETFL = "Y" (Prolia/Prolia); TRTEMFL = "Y" and TRT2EMFL = "Y" (Adverse Events).

The most common TEAEs with severities of Grade 3 or greater occurred in the SOCs for Injury, poisoning and procedural complications (HLX14 6 (2.3); EU-Prolia 4 (1.6)), Nervous system disorders (HLX14 4 (1.6); EU-Prolia 3 (1.2)), and Infections and infestations (HLX14 4 (1.6); EU-Prolia 2 (0.8) (Table 36). Patients with TEAEs of Grade 3 or greater where the TEAE was also a SAE are discussed in the in the section on SAEs. Patients with TEAEs that were also not SAEs were rare events and/or not associated with known toxicities of denosumab.

Table 36: Summary of Treatment Emergent Adverse Events ≥Grade 3 by SOC and PT (Main Period)

Patients[a] experiencing ≥1:	Main Period	
System Organ Class **Preferred Term**	**HLX14 N=256 n (%)**	**EU-Prolia N=258 n (%)**
Total patients with at least 1 TEAE ≥Grade 3	**25 (9.8)**	**19 (7.4)**
Injury, poisoning and procedural	**6 (2.3)**	**4 (1.6)**
Humerus fracture	2 (0.8)	0 (0.0)
Concussion	1 (0.4)	0 (0.0)
Femoral neck fracture	1 (0.4)	0 (0.0)
Lumbar vertebral fracture	0 (0.0)	1 (0.4)
Meniscus injury	1 (0.4)	0 (0.0)
Patella fracture	0 (0.0)	1 (0.4)
Spinal compression fracture	0 (0.0)	1 (0.4)
Thoracic vertebral fracture	1 (0.4)	0 (0.0)
Toxicity to various agents	0 (0.0)	0 (0.0)
Nervous system disorders	**4 (1.6)**	**2 (1.2)**
Cerebral infarction	1 (0.4)	1 (0.4)
Transient ischaemic attack	1 (0.4)	1 (0.4)
Cerebral hypoperfusion	1 (0.4)	0 (0.0)
Intracranial aneurysm	1 (0.4)	0 (0.0)
Lacunar infarction	1 (0.4)	0 (0.0)
Syncope	0 (0.0)	1 (0.4)

Patients[a] experiencing ≥1:	Main Period	
System Organ Class **Preferred Term**	**HLX14** **N=256** **n (%)**	**EU-Prolia** **N=258** **n (%)**
Infections and infestations	**4 (1.6)**	**2(0.8)**
Appendicitis	1 (0.4)	1 (0.4)
Complicated appendicitis	1 (0.4)	0 (0)
Gastroenteritis	1 (0.4)	0 (0)
Pneumonia	0 (0)	1 (0.4)
Septic shock	0 (0)	1 (0.4)
Urinary tract infection	1 (0.4)	0 (0)
Musculoskeletal/connective tissue	**3 (1.2)**	**3 (1.2)**
Rotator cuff syndrome	1 (0.4)	1 (0.4)
Intervertebral disc protrusion	0 (0.0)	1 (0.4)
Lumbar spinal stenosis	1 (0.4)	0 (0.0)
Spinal osteoarthritis	1 (0.4)	0 (0.0)
Synovitis	0 (0.0)	1 (0.4)
Gastrointestinal disorders	**1 (0.4)**	**3 (1.2)**
Haemorrhoids	0 (0.0)	2 (0.8)
Gastritis	0 (0.0)	1 (0.4)
Large intestine polyp	1 (0.4)	0 (0.0)
Cardiac disorders	**1 (0.4)**	**2 (0.8)**
Coronary artery disease	1 (0.4)	1 (0.4)
Angina pectoris	0 (0.0)	1 (0.4)
Ear and labyrinth disorders	**2 (0.8)**	**0 (0.0)**
Meniere's disease	1 (0.4)	0 (0.0)
Vertigo positional	1 (0.4)	0 (0.0)
Eye disorders	**2 (0.8)**	**0 (0.0)**
Cataract	1 (0.4)	0 (0.0)
Neovascular age-related macular degen	1 (0.4)	0 (0.0)
Metabolism and nutrition disorders	**1 (0.4)**	**1 (0.4)**
Hyperlipidaemia	1 (0.4)	0 (0.0)
Hypokalaemia	0 (0.0)	1 (0.4)
Blood and lymphatic system disorders	**1 (0.4)**	**0 (0.0)**
Anaemia	1 (0.4)	0 (0.0)
Hepatobiliary disorders	**0 (0.0)**	**1 (0.4)**
Hepatic function abnormal	0 (0.0)	1 (0.4)
Neoplasms benign/malignant	**0 (0.0)**	**1 (0.4)**
Cervix carcinoma	0 (0.0)	1 (0.4)
Renal and urinary disorders	**1 (0.4)**	**0 (0.0)**
Ureterolithiasis	1 (0.4)	0 (0.0)

Patients[a] experiencing ≥1:	Main Period	
System Organ Class **Preferred Term**	**HLX14** **N=256** **n (%)**	**EU-Prolia** **N=258** **n (%)**
Reproductive system and breast	**0 (0.0)**	**1 (0.4)**
Uterine polyp	0 (0.0)	1 (0.4)

[a]For each category, patients are included only once, even if they experienced multiple events in the same category
Source: Reviewer's Table, Source: OCS Analysis Studio, Safety Explorer. Adverse events missing severity/toxicity grades are not included in the above table. Filters: TRTSEQA = "HLX14 - HLX14" and SAFETFL = "Y" (HLX14/HLX14); TRTSEQA = "Prolia - HLX14" and SAFETFL = "Y" (Prolia/HLX14); TRTSEQA = "Prolia - Prolia" and SAFETFL = "Y" (Prolia/Prolia); TRTEMFL = "Y" and TRT2EMFL = "Y" and AETOXGRN = ("Grade 3", "Grade 4", or "Grade 5") (Adverse Events).

Adverse Events of Special Interest

For this review, an Adverse Events of Special Interest (AESI) was defined as any TEAE for the following conditions identified in the denosumab labeling under Warning and Precautions. The AESIs for this review are hypersensitivity including anaphylactic reactions, hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, vertebral fractures, and serious infections including skin infections.

Hypersensitivity including anaphylactic reactions

The OND Custom Medical Query (OCMQ) for Hypersensitivity using the MedDRA-Based Adverse Event Diagnostics (MAED) tool identified Preferred Terms associated with hypersensitivity (Table 37). Patient 1139028 in the Main Period receiving HLX14 developed an Anaphylactic reaction. An IR was sent to the Applicant and response was received on January 23, 2025. Per the investigator, the patient experienced an "allergic reaction" to Celecoxib and not an "anaphylactic reaction" as originally reported. The patient presented with symptoms of abdominal pain and pruritus and the symptoms disappeared after she discontinued taking Celecoxib. Based on the explanation received regarding this patient, there were no events of anaphylaxis. A review of the other patients associated with the Preferred Terms flagged during the OCMQ for Hypersensitivity did not identify any severe hypersensitivity reactions in either treatment group during the Main Period or Extension Period.

Table 37: Preferred Terms flagged using OCMQ for Hypersensitivity

Narrow OCMQ Term Preferred Term	**HLX14** **N=256** **n (%)**	**EU-Prolia** **N-258** **n (%)**
Hypersensitivity	**6 (2.3)**	**11 (4.3)**
Anaphylactic reaction	1 (0.4)	0 (0.0)
Dermatitis	1 (0.4)	1 (0.4)
Dermatitis atopic	1 (0.4)	0 (0.0)
Gingival swelling	1 (0.4)	0 (0.0)
Pruritus	1 (0.4)	2 (0.8)
Swelling of eyelid	1 (0.4)	0 (0.0)
Conjunctivitis allergic	0 (0.0)	2 (0.8)
Dermatitis allergic	0 (0.0)	1 (0.4)
Eczema	0 (0.0)	3 (1.2)
Rhinitis allergic	0 (0.0)	2 (0.8)
Urticaria papular	0 (0.0)	1 (0.4)

Source: Reviewer's Table, OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "HLX14" and SAFFL = "Y" (HLX14); TRT01A = "Prolia" and SAFFL = "Y" (Prolia); TRT1EMFL = "Y" (Adverse Events)

Injection site reactions (ISR)

Patients were monitored by the Investigator after administering the study drug. The duration of observation was determined by the Investigator based on the patient's condition, but typically for no more than 30 minutes. The Investigator recorded any observed ISR in the patient's medical records. If associated symptoms occurred after the patient returned home, they could either contact the Investigator immediately or report the issue at the next scheduled visit.

Injection site reactions were identified in 1 (0.4%) patient in the HLX14 arm and 2 (0.8%) patients in the EU-Prolia arm during the Main Period (Table 38). There were no injection site reactions reported during the Extension Period. Overall, injection site reactions were rare.

Table 38: Summary of Injection Site Reaction by System Organ Class and Preferred Term in the Main Period

System Organ Class **Preferred Term**	**HLX14** **N=256** **n (%)**	**EU-Prolia** **N=258** **n (%)**
Patients with at least one injection site reaction	**1 (0.4)**	**2 (0.8)**

Skin and subcutaneous tissue disorders	**0 (0)**	**2 (0.8)**
Erythema	**0 (0)**	**2 (0.8)**
General disorders/administration site condition	**1 (0.4)**	**0 (0)**
Injection site pruritus	**1 (0.4)**	**0 (0)**

Source: Reviewer's Table from CSR Table 14.3.1.9.1

Hypocalcemia and other Metabolic Labs of Special Interest

Denosumab can cause hypocalcemia and disturbances in bone-related mineral levels (i.e., reduced phosphorous and magnesium) and was associated with a higher incidence of anemia in the US-Prolia post-menopausal osteoporosis indication registration trial. The US-Prolia labeling advises monitoring of calcium, phosphorous and magnesium within 14 days of injection. Therefore, this review includes analyses of those laboratory parameters. The risk of hypocalcemia is greater in patients with severe renal impairment (i.e., glomerular filtration rate <30 mL/min), and this study excluded patients with an estimated glomerular filtration rate <30 mL/min.

During the Main Period, patients received a study drug injection at study day 0 and a second injection 6 months later at study day 181. All patients were required to have a normal corrected calcium level at baseline and to receive daily calcium and vitamin D supplements from screening to end of study. The expected calcium nadir is at 2 weeks post denosumab injection. During Study 002-pmop301 calcium labs were not collected at 2 weeks post injection and the closest time point to 2 weeks was Week 4 (Table 39). Shift analyses were performed using uncorrected calcium and compared to baseline at Week 4 and Week 26 of the Main Period. The median change in calcium was low and comparable in both arms.

Table 39: Median change from baseline in serum calcium (mg/dL) following first study drug administration during Main Period

	HLX14 (N=256)	EU-Prolia (N=258)
Change from Baseline to Month 1 (mg/dL)		
Mean (SD)	-0.2 (0.48)	-0.2 (0.49)
Median (Min, Max)	-0.2 (-1.4, 2)	-0.2 (-1.56, 1.84)
Change from Baseline to Month 6 (mg/dL)		
Mean (SD)	0.0 (0.48)	0.0 (0.44)
Median (Min, Max)	0.0 (-1.04, 1.4)	0.0 (-1.16, 1.16)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'; Column Variable 1: TRT01A (Actual Treatment for Period 01).

The incidence of patients with hypocalcemia (i.e., serum calcium below the lower limit of

normal) during treatment was similar between the two treatment groups. Most of these shifts occurred during the first two weeks of treatment. After the second denosumab injection at week 26, the incidence of hypocalcemia was rare. (Table 40).

Table 40: Patients with shift in serum calcium to below the lower limit of normal (<LLN) after first and second study drug administration during Main Period

	HLX14 (N=256) n (%)	EU-Prolia (N=258) n (%)
At Any Time During TP1	17 (6.6)	26 (10.1)
Following First study drug Injection in Main Period		
Week 04	7 (2.7)	12 (4.7)
Week 13	5 (2.0)	8 (3.1)
Week 26	1 (0.4)	2 (0.8)
Following Second study drug Injection in Main Period		
Week 39	6 (2.3)	4 (1.6)
Week 52	1 (0.4)	1 (0.4)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'; Column Variable 1: TRT01A (Actual Treatment for Period 01).

During the Extension Period, patients received their third and final dose of study drug at Week 52 (Month 12). Calcium levels were checked at Month 15 and Month 18. The median change in calcium was low and comparable in all arms (Table 41).

Table 41: Serum calcium change from Extension Period baseline (i.e., Month 12) to Month 15 and Month 18

	EU-Prolia/ HLX14 (N=110)	EU-Prolia/ EU-Prolia (N=110)	HLX14/ HLX14 (N=220)
Change from Baseline (Month 12) to Month 15 (3 Months post-dose) (mg/dL)			
Mean (SD)	-0.2 (0.43)	-0.1 (0.44)	-0.2 (0.46)
Median (Min, Max)	-0.2 (-1.2, 1.36)	-0.1 (-1.2, 1.04)	-0.2 (-1.4, 1.32)
Change from Baseline (Month 12) to Month 18 (6 Months post-dose) (mg/dL)			
Mean (SD)	-0.1 (0.49)	-0.1 (0.40)	-0.1 (0.46)
Median (Min, Max)	-0.1 (-2.08, 1.04)	-0.1 (-1.24, 1.24)	-0.1 (-1.48, 1.16)

Source: OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: SAFETFL = 'Y'; Column Variable 1: TRTSEQA (Actual Sequence of Treatments).

Hemoglobin, Magnesium Phosphorus Levels

The incidence of transitions from normal at baseline to below the normal range for serum hemoglobin, magnesium, and phosphorous were similar between treatment arms during the Main Period (Table 42) and the Extension Period (Table 43). There were no meaningful differences in the incidence of anemia, hypomagnesemia, hypophosphatemia, during the study.

Table 42: Incidence of shifts to below the limit of normal in hemoglobin, magnesium, and phosphate during Main Period

	HLX14 (N=256)	Prolia (N=258)
Laboratory Test		
Hemoglobin (g/L)		
Baseline Normal Shift to Low	19 (7.4)	18 (7.0)
Magnesium (mmol/L)		
Baseline High Shift to Low	1 (0.4)	1 (0.4)
Baseline Normal Shift to Low	22 (8.6)	19 (7.4)
Phosphate (mmol/L)		
Baseline High Shift to Low	1 (0.4)	0
Baseline Normal Shift to Low	40 (15.6)	51 (19.8)

Source: OCS Analysis Studio, Custom Table Tool

Table 43: Patients with serum hemoglobin, magnesium, or phosphate values less than the lower limit of normal (<LLN) at start of Extension Period (Month 12) and at conclusion of Extension Period (Month 18)

	EU-Prolia/ HLX14 (N=110) n (%)	EU-Prolia/ EU-Prolia (N=110) n (%)	HLX14/ HLX14 (N=220) n (%)
Hemoglobin (g/L)			
Start of TP 2 (Week 52)	5 (4.5)	7 (6.4)	8 (3.6)
End of TP 2 (Week 78)	9 (8.2)	11 (10.0)	10 (4.5)
Magnesium (mmol/L)			
Start of TP 2 (Week 52)	2 (1.8)	7 (6.4)	8 (3.6)
End of TP 2 (Week 78)	4 (3.6)	6 (5.5)	9 (4.1)
Phosphate (mmol/L)			
Start of TP 2 (Week 52)	8 (7.3)	3 (2.7)	5 (2.3)

	EU-Prolia/ HLX14 (N=110) n (%)	EU-Prolia/ EU-Prolia (N=110) n (%)	HLX14/ HLX14 (N=220) n (%)
End of TP 2 (Week 78)	2 (1.8)	7 (6.4)	13 (5.9)

Source: OCS Analysis Studio, Custom Table Tool

Osteonecrosis of the Jaw

No events of osteonecrosis of the jaw were identified.

Fractures

Radiographs of the vertebrae were done at Baseline, Week 52, and Week 78 (lumbar vertebrae with cervical, thoracic vertebrae and other parts of the vertebrae determined by the Investigator) and hip. If the patient had any signs of fracture during the study, radiographs could be performed.

The OND Custom Medical Query (OCMQ) for Fracture using the MedDRA-Based Adverse Event Diagnostics (MAED) tool identified Preferred Terms associated with fractures (Table 44 and Table 45). The number of patients with the flagged Preferred Terms for Fracture are balanced between arms within treatment periods. Patients with SAEs of fracture are discussed with Summary Narratives in the Section on SAEs. A review of the other patients associated with the Preferred Terms flagged during the OCMQ for Fracture did not identify any severe nontraumatic fractures in either treatment group during the Main Period or Extension Period.

Table 44: Preferred Terms flagged using OCMQ for Fracture (Main Period)

Narrow OCMQ Term Preferred Term	HLX14 N=256 n (%)	EU-Prolia N-258 n (%)
Fracture	**10 (3.9)**	**10 (3.9)**
Spinal compression fracture	3 (1.2)	6 (2.3)
Humerus fracture	2 (0.8)	0 (0.0)
Thoracic vertebral fracture	2 (0.8)	0 (0.0)
Femoral neck fracture	1 (0.4)	0 (0.0)
Forearm fracture	1 (0.4)	0 (0.0)
Rib fracture	1 (0.4)	1 (0.4)
Scapula fracture	1 (0.4)	0 (0.0)
Ankle fracture	0 (0.0)	1 (0.4)
Lumbar vertebral fracture	0 (0.0)	1 (0.4)
Patella fracture	0 (0.0)	1 (0.4)

Source: OCS Analysis Studio, Safety Explorer
Filters: TRT01A = "HLX14" and SAFFL = "Y" (HLX14); TRT01A = "Prolia" and SAFFL = "Y" (Prolia); TRT1EMFL = "Y" (Adverse Events).

Table 45: Preferred Terms flagged using OCMQ for Fracture (Extension Period)

Narrow OCMQ Term Preferred Term	EU-Prolia/ HLX14 N=110 n (%)	EU-Prolia/ EU-Prolia N=110 n (%)	HLX14/ HLX14 N=220 n (%)
Fracture	**5 (4.5)**	**2 (1.8)**	**7 (3.2)**
Spinal compression fracture	4 (3.6)	2 (1.8)	5 (2.3)
Fractured sacrum	0 (0.0)	0 (0.0)	1 (0.5)
Lumbar vertebral fracture	0 (0.0)	0 (0.0)	1 (0.5)
Radius fracture	2 (1.8)	0 (0.0)	0 (0.0)
Rib fracture	1 (0.9)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer

Serious infections including skin infections

Serious infections were rare during Study 002-PMOP301. The OND Custom Medical Query (OCMQ) for Serious infection using the MedDRA-Based Adverse Event Diagnostics (MAED) tool did not identify additional patients with serious infections who were not previously discussed in the SAE section.

Dermatologic reactions

Severe dermatologic reactions were rare during Study 002-PMOP301. There were no patients with Preferred Terms within the Skin and subcutaneous tissue disorders SOC that were Grade 3 or greater in severity.

There were no meaningful differences in terms of AESI between arms on the Main and Extension Periods.

Dropouts and/or Discontinuations

Three patients discontinued from Study 002-PMOP301 due to an adverse event. All were during the Main Period and in the EU-Prolia arm. Preferred terms leading to early discontinuation were Cervix carcinoma, Toothache, and Periodontitis/Gingival cyst. None appear to be related to study drug and there were no meaningful differences between treatment groups.

6.3.3. Additional Safety Evaluations

The results of the safety review of PK Similarity Study, Study HLX14-001 are summarized in Table 46. A single dose of 60 mg of investigational product was administered to all subjects and the exposure in terms of total dose received was the same (60 mg) across all arms. There were no reported deaths during the study. One subject in the US-Prolia arm experienced a SAE coded with Preferred Term of synovitis. The adverse events by grading were comparable between arms. There were no reported discontinuations from the study due to an adverse event. AESI were rare with events of hypocalcemia being the most common. There were no trends in laboratory

values, vital signs, physical exam findings, or ECGs that suggest a new safety signal.

Table 46: HLX14-001 (Part 2) Summary of Safety Events

Patients[a] Experiencing ≥ 1:	HLX14 N=58 n (%)	US-Prolia N=57 n (%)	EU-Prolia N=56 n (%)	CN-Prolia N=57 N (%)
Exposure (mg)	60	60	60	60
Deaths	0 (0)	0 (0)	0 (0)	0 (0)
Serious Adverse Events	0 (0)	1 (1.8)	0 (0)	0 (0)
Adverse Events Grades 1-5 Grades 3-5	 58 (100) 3 (5.2)	 57 (100) 6 (10.6)	 56 (100) 6 (10.7)	 57 (100) 2 (3.5)
Discontinuations due to AE	0 (0)	0 (0)	0 (0)	0 (0)
AESI Blood calcium decreased Hypocalcaemia Arthritis infective	 3 (5.2) 1 (1.7) 0 (0)	 7 (12.3) 1 (1.8) 1 (1.8)	 7 (12.5) 2 (3.6) 0 (0)	 8 (14.0) 1 (1.8) 0 (0)

[a]Patients are included only once per category, even if they experienced multiple events in the same category.
Source: Reviewer's Table. Adapted from Table14.1.6.1, ADAE dataset

For Study 002-PMOP301, there were no trends in laboratory values, vital signs, physical exam findings, or ECGs that suggest a new safety signal.

The review of Study 002-PMOP301 and Study 002-PMOP301 did not identify any clinically meaningful differences in terms of safety between HLX-14 and US-Prolia, or EU-Prolia. The results support a demonstration that there are no clinically meaningful differences between HLX14 and US-Prolia

6.4. Clinical Conclusions on Immunogenicity

All patients in the safety population had immunogenicity data collected throughout the study. During the Main Period, 14 patients receiving HLX14 and 17 receiving EU-Prolia were positive prior to receiving study drug, whereas 28 patients were positive for ADA after receiving HLX14 and 35 patients after receiving EU-Prolia. None of the patients receiving HLX14 were positive for neutralizing antibodies, while two patients receiving EU-Prolia were positive for neutralizing antibodies.

There was one patient reported with grade 1 adverse event of anaphylaxis. An information request was sent to the applicant to obtain more information. Based on the response, this event was unlikely to be drug related. The patient was receiving HLX14 in the Main period and complained of abdominal pain and pruritus 3 months after receiving the second dose of HLX14. During this time, the patient was taking Celecoxib once daily for 3 days. The investigator reported the adverse event as anaphylactic

reaction and advised the patient to discontinue taking the Celecoxib and her symptoms resolved.

During the single transition extension period, 17 patients who were switched from EU-Prolia to HLX14 and 15 patients who remained on EU-Prolia were positive for ADAs at baseline and during the Main Treatment Period. Of these, there was one patient positive for neutralizing antibodies. At the end of the Extension Period, 17 patients who were switched from EU-Prolia to HLX14 and 15 patients who remained on EU-Prolia were positive for ADAs at baseline and during all of both the Main and Treatment Periods. Of these there was one patient positive for neutralizing antibodies. There was no increase in the incidence of ADAs or Neutralizing antibodies during the Extension Period, except one patient in the arm that stayed on the biosimilar had an additional ADA. There were no documented episodes of anaphylaxis, or other serious hypersensitivity reaction during the Extension Period.

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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 HLX14, US-Prolia and US-Xgeva share identical primary structures and comparable secondary and tertiary structures. Functional assays showed similarity among HLX14, US-Prolia and US-Xgeva with respect to pharmacologic activity. There were no meaningful differences between HLX14 and US-Prolia in the PK similarity study.

The comparative clinical study showed no meaningful difference in PK, efficacy, safety, or immunogenicity between HLX14 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 HLX14 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 HLX14 at Week 52 was well tolerated with no meaningful impact on PK, efficacy, or safety. At six months post-transition (i.e., Week 78), the median percentage change from baseline in lumbar spine BMD was similar in the two treatment groups. There was no increase in ADA titers or incidence of NAbs after transitioning from US-Prolia to HLX14.

The Applicant provided sufficient justification that HLX14 can be expected to produce the same clinical result as US-Prolia and US-Xgeva 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. The applicant also referred to their HLX14 development data to further support their justification.

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 HLX14 exhibits the same pharmacologic activity as US-Prolia and US-Xgeva and has identical primary structure to US-Prolia and US-Xgeva. The comparative analytical assessment support HLX14 is highly similar to US Prolia and US-Xgeva. Furthermore, there was no meaningful difference in the effect of HLX14 and US-Prolia on the 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 HLX14 has 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 (PK)

The applicant provided adequate justification that HLX14 is 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 HLX14 development program, immunogenicity was evaluated in populations considered sensitive for detecting clinically meaningful differences: female subjects with PMO and healthy subjects. Immunogenicity was found to be similar when comparing HLX14 and US-Prolia in the PK Similarity Study HLX14-001 in healthy subjects, and between HLX14 and US -Prolia in the comparative clinical study, Study 002-PMOP301, in PMO women. The applicant provided adequate justification that HLX14 is 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, Study 002-PMOP301, which was conducted in patients with postmenopausal osteoporosis (PMO). Supportive safety information was also available from the PK similarity study, HLX14-001. The Applicant provided adequate justification that HLX14 is 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 HLX14 and US-Prolia or 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 HLX14 and US-Prolia and US-Xgeva and the results from the comparative clinical study (Study 002PMOP301) to support their justification. The Applicant also described that the

results from the single transition included in Study 002PMOP301 provided supportive evidence of a low immunogenic risk and no safety concerns with switching between HLX14 and US-Prolia or US-Xgeva.

FDA considers the risk of a clinically impactful immunogenic response when alternating or switching between HLX14 and US-Prolia or US-Xgeva 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 HLX14 and US-Prolia or US-Xgeva was considered unnecessary to support a demonstration of interchangeability for HLX14.

In summary, the data and information provided by the Applicant are sufficient to demonstrate that HLX14 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 HLX14 and US-Prolia, or HLX14 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 HLX14 is highly similar to US-Prolia and US-Xgeva notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between HLX14 and US-Prolia, or HLX14 and US-Xgeva, in terms of safety, purity, and potency. In addition, the totality of evidence submitted in the application sufficiently demonstrates that HLX14 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 HLX14 and US-Prolia or HLX14 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 HLX14 for the following indication(s) for which US-Prolia and US-Xgeva have been previously licensed and for which HLX14 has not been directly studied:

- Treatment to increase bone mass in men with osteoporosis at high risk for fracture
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for 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 HLX14 as an interchangeable biosimilar 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 HLX14 as a biosimilar to and interchangeable with US-Prolia and US-Xgeva for each of the following indication(s) for which the Applicant is seeking licensure of HLX14:

- Treatment of post-menopausal women with osteoporosis at high risk for fracture.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture,
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for 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 HLX14 for all indications for which US-Prolia and US-Xgeva are licensed.

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7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, denosumab-nxxp, was found to be conditionally accepted by the Agency.

7.2. Proprietary Name

The proposed proprietary names for HLX14 are conditionally approved as Bildyos for HLX14 60 mg (denosumab-nxxp in a 60 mg/mL PFS and 60 mg/mL vial) and Bilprevda for HLX 120 mg (denosumab-nxxp in a 120 mg/1.7 mL vial). These names have been reviewed by DMEPA, who concluded the names were acceptable.

7.3. Other Labeling Recommendations

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

For Bildyos and Bilprevda, text throughout the Full Prescribing Information were made to align with the reference product Prolia and Xgeva, respectively, and language used when referring to a denosumab biosimilar. "Bildyos", "Bilprevda", "Denosumab-nxxo", "denosumab" or "denosumab products" were used in place of Prolia or Xgeva as applicable.

For Bildyos, major changes to the draft labeling were made to the following sections of the Prescribing Information:

- 1 INDICATIONS AND USAGE/ 1.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture: (b) (4) was changed to "In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures *[see Clinical Studies (14.1)]*. The sentence refers to clinical studies that were conducted with the reference product Prolia, not the proposed product Bildyos; therefore, the reference product's proper name "denosumab" should be used for the denosumab biosimilar product.
- 1 INDICATIONS AND USAGE/ 1.4 Treatment of Bone Loss in Men Receiving Androgen Deprivation Therapy for Prostate Cancer: In the sentence "In these patients denosumab (b) (4) also reduced the incidence of vertebral fractures *[see Clinical Studies (14.4)]*", (b) (4) was deleted because the sentence refers to clinical studies conducted with the reference product Prolia; therefore, the reference product's proper name "denosumab" should be used.
- 2 DOSAGE AND ADMINISTRATION/ subsection 2.1 subheading title changed

from [redacted] to "Pregnancy Testing Prior to Initiation of Bildyos" to align with reference product labeling.

- 2 DOSAGE AND ADMINISTRATION/ 2.3 Recommended Dosage: "Bildyos should be administered by a healthcare [redacted]" was updated to "Bildyos should be administered by a healthcare provider" to include terminology commonly used in labeling when referring to healthcare individuals or prescribers.
- 2 DOSAGE AND ADMINISTRATION/ 2.4 Preparation and Administration/ *Instructions for Administration of Prefilled Syringe with Needle Safety Guard*: Added "Bildyos" before Prefilled Syringe to include proprietary name in the subheading title. Added "Choose and injection site" under Step 2. The Applicant included illustrations for pinching of the skin and injection angle for a subcutaneous injection; both steps are familiar to healthcare providers and included in text. The section was simplified by removing common knowledge and redundancy.
- 5 WARNINGS AND PRECAUTIONS/ 5.2 Drug Products with Same Active Ingredient: Deleted [redacted] to align with the reference product.
- 5 WARNINGS AND PRECAUTIONS/ 5.6 Multiple Vertebral Fractures (MVF) Following Discontinuation of Treatment: For Bildyos labeling, the Applicant [redacted] When clinical studies or specific data derived from studies with the reference product are described in biosimilar product labeling; the reference product's proper name (denosumab) is use; therefore, [redacted] was deleted.
- 5 WARNINGS AND PRECAUTIONS/ 5.11 Hypercalcemia in Pediatric Patients with Osteogenesis Imperfecta: Updated cross reference from [redacted] to see "Use in Specific Population (8.4)" to refer to the main heading name and to be consistent with Prolia.
- 6 ADVERSE REACTIONS: reordered listing of adverse reactions listed in Section 5 and included Hypersensitivity based on Prolia S-219 approved on May 22, 2025.
- 6 ADVERSE REACTIONS/ 6.1 Clinical Trials Experience: Added "The most common adverse reactions reported with denosumab in patients with patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis" to be consistent with Prolia.
- 8 USE IN SPECIFIC POPULATIONS/ 8.4 Pediatric Use: Added "Based on results from animal studies, denosumab may negatively affect long-bone growth and dentition in pediatrics below the age of 4 years" for consistency with Prolia S-213 approved on March 5, 2024. Added "Safety and effectiveness were not demonstrated for the treatment of glucocorticoid-induced osteoporosis in one multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted in 24 pediatric patients with glucocorticoid-induced osteoporosis, aged 5 to 17 years, evaluating change from baseline in lumbar spine BMD Z-score" for consistency with Prolia S-219 approved on May 22, 2025.
- 10 OVERDOSAGE: Deleted Section 10 as it should not be included if there are

no overdosage information and to be consistent with Prolia.

- 11 DESCRIPTION: Inactive ingredients revised by using established names per USP/NF monograph titles and reordered to appear in alphabetical order.
- 12 CLINICAL PHARMACOLOGY/ 12.3 Pharmacokinetics: included main subheadings Absorption, Distribution, and Elimination per FDA's Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2016) and to be consistent with Prolia USPI.
- 14 CLINICAL STUDIES/ 14.1 Treatment of Postmenopausal Women with Osteoporosis: For Figure 1, the legend was updated (b) (4) to "Denosumab", the reference product's proper name.
- 16 HOW SUPPLIED/STORAGE AND HANDLING: Added NDC numbers (60 mg/mL PFS) and 78206-194-01 (60 mg/mL vial). Added " (b) (4) direct light" to protect product from direct light.
- 17 PATIENT COUNSELING INFORMATION/ Drug Product with Same Active Ingredient: Updated language to state "Advise patients that if they receive Bildyos, they should not receive other denosumab products concomitantly" to be consistent with Prolia.

For Bilprevda, major changes to the draft labeling were made to the following sections of the Prescribing Information:

- 2 DOSAGE AND ADMINISTRATION/ 2.1 Important Administration Instructions: Added the statement "Bilprevda should be administered by a healthcare provider" to provide specific recommendation for the administration of this product and to be consistent with reference product Xgeva.
- 2 DOSAGE AND ADMINISTRATION/ 2.5 Preparation and Administration: Added "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit" per 21 CFR 201.57(c)(3)(iv).
- 5 WARNINGS AND PRECAUTIONS/ 5.1 Drug Products with Same Active Ingredient: Deleted (b) (4) to align with the reference product Xgeva.
- 6 ADVERSE REACTIONS/ 6.1 Clinical Trials Experience/ *Osteonecrosis of the Jaw (ONJ)*: Added "Study 20140114 (NCT03301857) was a 5-year long term follow-up study for patients (n=85) who completed Study 20062004. In Study 20062004 and Study 20140114 combined, ONJ was confirmed in 7% of patients who received denosumab (median time on trial 62.2 months (range 0 – 173). The combined patient-year adjusted incidence (number of events per 100 patient years) of confirmed ONJ was 0.2% during the first year of treatment, 1.5% in the second year, 1.8% in the third year, 2.1% in the fourth year, 1.4% in the fifth year, and 1.5% thereafter *[see Warnings and Precautions (5.4)]"* for consistency with Xgeva S-222 approved May 30, 2025.
- 6 ADVERSE REACTIONS/ 6.1 Clinical Trials Experience/ *Atypical Subtrochanteric and Diaphyseal Fracture*: Added "In the pooled analysis of Study 20062004 and Study 20040215, atypical femoral fracture was observed in 0.9% of patients who received denosumab (median number of doses received: 33;

range: 4-138 doses). In Study 20062004 and Study 20140114, the combined incidence of confirmed atypical femoral fracture was 1.3% of patients who received denosumab *[see Warnings and Precautions (5.5)]*" for consistency with Xgeva S-222 approved May 30, 2025.

- 12 CLINICAL PHARMACOLOGY/ 12.6 Immunogenicity: Replaced (b) (4) with "Using an electrochemiluminescent bridging immunoassay, less than 1% (55 out of 8113) of patients treated with denosumab for up to 5 years tested positive for binding antibodies (including pre-existing, transient, and developing antibodies). None of the patients tested positive for neutralizing antibodies, as was assessed using a chemiluminescent cell-based in vitro biological assay. There was no identified clinically significant effect of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of denosumab" to align with Xgeva S-222 approved May 30, 2025.
- 16 HOW SUPPLIED/ STORAGE AND HANDLING: include NDC numbers 78206-195-01 [120 mg/1.7 mL (70 mg/mL) vial]. Added "Prior to administration, Bilprevda may be allowed to reach room temperature (up to 25°C/77°F) in the original container" for clarity regarding storage of unused product.
- 17 PATIENT COUNSELING INFORMATION/ Drug Product with Same Active Ingredient: Updated language to state "Advise patients that if they receive Bilprevda, they should not receive other denosumab products concomitantly" to be consistent with Xgeva.

Authors:

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Shivangi Vachhani, MD
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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 Module 1.3.4 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

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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.

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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, denosumab products, Jubbonti and Wyost, have been approved as interchangeable biosimilars and have qualified for a period of FIE. FDA has previously determined that FIE for the Jubbonti and Wyost products will expire on October 29,2025. Therefore, because HLX14 will be approved first as a biosimilar (and not as interchangeable), this biologic will be considered to have a new active ingredient.

At a meeting with the Pediatric Review Committee (PeRC) on December 20, 2022, the PeRC agreed to the Applicant’s plan to request a partial waiver and deferral for pediatric studies as outlined in the Agreed iPSP. Refer to minutes of 12/20/22 filed to PIND

153872 and finalized in DARRTS on 01/18/23.

There is a lack of pediatric information for the following indications in the reference product labeling. For the following indications and populations, and PREA requirements were waived for, or inapplicable to, US-Prolia or US-Xgeva, and therefore the Applicant is not required to submit a pediatric assessment for them:

US-Prolia:

- Treatment of post-menopausal 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
- Treatment of glucocorticoid-induced osteoporosis (b) (4) (b) (4) at high risk for fracture

US-Xgeva:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.
- Treatment of (b) (4) skeletally mature (b) (4) (b) (4) with giant cell tumor of the 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 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 16 years) based on a demonstration of biosimilarity and providing adequate scientific justification to support extrapolation based on data and information to support licensure. Refer to Section 7.6 for review of the assessment.

In addition, the Applicant refers to the deferral of submission of required pediatric study for the treatment of pediatric patients aged 5 to 17 years with glucocorticoid induced osteoporosis (GIOP) at high risk for fracture. Therefore, the Applicant initially requested a deferral for pediatric patients ages 5 to 17 years of age for the treatment of GIOP indication. This was discussed at the PeRC meeting on 7/18/25. However, a deferral will not be necessary because the PREA PMR for US-Prolia has been fulfilled as of May 22, 2025, and the appropriate pediatric language has been added to Subsection 8.4 Pediatric Use of Section 8 USE IN SPECIFIC POPULATIONS of the US-Prolia label 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 fulfills PREA requirements for this indication by including the relevant pediatric information in the PI and MedGuide for this

product to align with changes made by US-Prolia.

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11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

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

On August 30, 2024, Shanghai Henlius Biotech, Inc. submitted a BLA with a proposed REMS for Bildyos that consisted of a CP and timetable for submission of assessments. The Agency sent comments requesting the Applicant submit all REMS materials in the acceptable formats and requesting editorial edits to the Bildyos REMS Document and revisions to the Supporting Document. The Applicant submitted an amended REMS on December 4, 2024, May 15, 2025, and June 23, 2025.

The Division of Risk Management (DRM) reviewed the REMS and found the Bildyos REMS, submitted on August 30, 2024, and amended on December 4, 2024, May 15, 2025, and June 23, 2025, acceptable. The Bildyos REMS is comparable to the Prolia REMS and is designed to communicate the same key risk messages and achieve the same level of patient safety.

The Bildyos REMS goal and objective are:

> The goal of the Bildyos REMS is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Bildyos. 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/1.73 m^2)
> > - Need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Bildyos in patients with advanced chronic kidney disease
>
> The REMS elements consist of a Communication plan (CP) and timetable for submission of assessments.

The Communication Plan 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 Bildyos REMS assessment plan was reviewed by the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) and found to be acceptable.

Authors:

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Yasmeen Abou-Sayed, PharmD.
Team Leader, DRM

11.2. Recommendations for Postmarket Requirements and Commitments

Not applicable.

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12. Division Director 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 HLX14 is biosimilar to US-Prolia and US-Xgeva. I also concur with the team's recommendation to provisionally determine that HLX14 meets 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 HLX14 meets 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 Bildyos and Bilprevda, as discussed in Section 1.7 above. Accordingly, I also concur with the review team's recommendation to provisionally determine that:

HLX14, 60 mg/mL injection for SC use in a single-dose vial and in a PFS meets the applicable standards for interchangeability with US-Prolia, 60 mg/mL injection for SC use in a single-dose vial and in a PFS, and HLX14, 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 HLX14 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 HLX14 as a biosimilar product (“Original 1”) and a provisional determination that HLX14 is an interchangeable biosimilar product (“Original 2”), as described in Section 1.7 above. The Applicant is expected to submit an amendment seeking approval of BLA 761444/Original 2 no more than six months prior to the expiration of exclusivity, or when the Applicant believes that BLA 761444/Original 2 will become eligible for approval.

Author:
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Division Director, Division of General Endocrinology

13. Appendices

13.1. Financial Disclosure

Covered Clinical Study 002PMOP301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 53		
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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The applicant provided certification on Form FDA 3454 to indicate that there were no financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of Study 1 HLX14-001 and Study 2 HLX14-002PMOP301, that there were no investigators who did not

provide any financial disclosure information, and that the investigators were not the recipients of significant payments of other sorts.

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13.2. Nonclinical Appendices

Not applicable because nonclinical study reports were not submitted.

13.3. Clinical Pharmacology Appendices

13.3.1. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For the PK similarity study HLX14-001 and the comparative clinical study HLX14-002-PMOP301, serum concentrations of study drugs from HLX14, EU-Prolia and US-Prolia were measured using a validated ELISA method.

The method validation entitled *VALIDATION OF AN ELISA METHOD FOR THE QUANTIFICATION OF HLX14 AND PROLIA IN HUMAN SERUM* in Human Serum and sample analysis for the study were performed at Shanghai Henlius Biologics Co., Ltd. (Shanghai, China). In this method, HLX14 and Prolia in human serum are captured by RANKL-His antigen ((b) (4) Cat. No. RALH5240, Lot: C172P1-21CGG1-ZF) and detected by HRP-conjugated goat anti-human Igκ ((b) (4) Cat. No. AP502P, Lot: 3750115). After a final wash step, a colorimetric signal produced by TMB reacting with the peroxide is measured at 450 nm with a reference at 630 nm subtracted by plate reader Softmax.

Table 47 shows the summary of the ELISA method validation and performance in quantification of HLX14, EU-Prolia and US-Prolia. During the review, an Information Request (IR) was sent on April 15th, 2025 seeking clarification regarding which Prolia (US or EU) was included in the validation report. Additionally, the review team requested several assay parameters of the Prolia product that was not included in the submitted validation report, including dilutional linearity and hook effect, specificity (target interference), stability, hemolytic matrix effect, and lipemic matrix effect.

The applicant responded on April 29th, 2025, indicating that EU-Prolia was used in the validation report. US-Prolia was used to evaluate the assay accuracy and Precision in their Assay Validation Report Addendum 01. They also referred to their Assay Validation Report Addendum 02, stating that bias differences between HLX14 and EU-Prolia, and HLX14 and US-Prolia are all within 10%. The applicant cited a white paper, "Current Perspectives on Ligand-Binding Assay Practices in the Quantification of Circulating Therapeutic Proteins for Biosimilar Biological Product Development," which states that a single PK bioanalytical method can be used in the PK similarity study if the

bioanalytical bias difference between products is within 10%. Based on the comparability results, there is no need to evaluate other assay parameters for US Prolia. FDA agrees with the applicant's justification.

Overall, this bioanalytical method was fully validated in accordance with the Bioanalytical Method Validation Guidance from the agency and is considered suitable for the assessment of serum concentrations of study drugs for the current BLA.

Table 47. Summary of bioanalytical method validation and in-study performance measurement of HLX14, EU-Prolia and US-Prolia

Bioanalytical method review summary	An ELISA method was used to quantify free study drug in serum of healthy subjects in Study HLX14-001 part II and patients in HLX14-002-PMOP301. Free study drug in serum samples was captured by RANKL-His antigen and detected by HRP-conjugated goat anti-human Igκ. After a final wash step, a colorimetric signal produced by tetramethylbenzidine (TMB) reacting with the peroxide is measured at 450 nm with a reference at 630 nm subtracted by plate reader Softmax. The method was fully validated over a range of 148.0 ng/mL to 9864.9 ng/mL for study drug in accordance with the Bioanalytical Method Validation Guidance from the agency.
Materials used for calibration curve & concentration	Matrix: The standard curve was prepared by spiking HLX14 with 100% pooled normal human serum Tested product: HLX14 Calibration concentration: 148.0 ng/mL (LLOQ), 394.6 ng/mL, 739.9 ng/mL, 1479.8 ng/mL, 3946.0 ng/mL, 7891.9 ng/mL, 9864.9 ng/mL (ULOQ).
Validated assay range	148.0 ng/mL to 9864.9 ng/mL
Material used for QCs & concentration	Matrix: The quality control samples were prepared by spiking HLX14 or Prolia with 100% pooled normal human serum Tested product: HLX14, EU-Prolia QC concentrations: 147.8 ng/mL (Prolia LLOQ), 148.0 ng/mL, (HLX14 LLOQ), 443.3 ng/mL (Prolia LQC), 443.9 ng/mL, (HLX14 LQC), 2463.0 ng/mL (Prolia MQC), 2466.2 ng/mL, (HLX14 MQC), 7388.9 ng/mL (Prolia HQC), 7398.7 ng/mL, (HLX14 HQC), and 9851.9 ng/mL (Prolia ULOQ), 9864.9 ng/mL (HLX14 ULOQ).
Minimum required dilutions (MRDs)	MRD: 1:200
Source & lot of reagents (LBA)	Capture: RANKL-His antigen; Lot: C172P1-21CGG1-ZF; Source: (b) (4) Primary Detection: HRP-conjugated goat anti-human Igκ; Lot: 3750115; Source: (b) (4) Prolia Lot: 00105340681/1137094B; Source: (b) (4) Pooled normal human serum Lot: 2021067-P16; Source: Henlius
Regression model & weighting	Fitting Formula: Four Parameters Y=D+(A-D)/{[1+(x/C)B]}

	Weighting factor: 1/Y2		
Validation Parameters	**Method Validation Summary**		**Acceptability**
Calibration curve performance during accuracy & precision Per BMV, At least 75% and minimum of 6 non-zero calibrators without anchor points and LBA: ±20% bias (±25% at lower limit of quantitation (LLOQ)), ≤ 20%CV	No of standard calibrators from LLOQ to upper limit of quantitation (ULOQ)	7	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ HLX14	–3.8 to 3.9%	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ HLX14	0.5-2.0%	Acceptable
QCs performance during accuracy & precision Per BMV, LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)	Cumulative accuracy (%bias) in 5 QCs HLX14 EU- Prolia US- Prolia	 -7.9% to 6.4% -4.8% to 8.1% -5.0% to 8.9%	Acceptable
	Inter-batch %CV HLX14 EU- Prolia US- Prolia	 2.4% to 11.4% 7.8% to 13.5% 3.2% to 8.2%	Acceptable
	Percent total error (TE) HLX14 EU- Prolia US- Prolia	 2.6% to 18.9% 9.9% to 21.6% 4.5% to 20.3%	Acceptable
Selectivity & matrix effect	The pooled serum samples had the %CV ≤ 25% and %bias within ± 25% which shows the viability of sample preparation. Nine out of ten individual serum samples prepared by HLX14 or EU-Prolia met the acceptance criteria. No matrix effect observed		Acceptable
Interference & specificity	Specificity was tested with RANKL-His interference. Soluble RANKL-His solutions at 2x0.2 ng/mL, 2x1.0		Acceptable

	ng/mL, 2x5.0 ng/mL and 2x20.0 ng/mL concentrations were mixed 1:1 with the samples spiked with HLX14 or EU-Prolia at concentrations of 2xULOQ (19729.7 ng/mL for HLX14 and 19703.7 ng/mL for Prolia), 2xLLOQ (296.0 ng/mL for HLX14 and 295.6 ng/mL for Prolia) and blank. Test samples were prepared in 5 aliquots and analyzed in duplicates. As a result, no interference was observed in the presence of up to 5.0 ng/mL of RANKL-His. The measurement of HLX14 and EU-Prolia was not interfered by RANKLHis (up to 5.0 ng/mL)	
Hemolysis effect	The pooled serum samples had the %CV ≤ 25% and %Bias within ± 25% which shows the viability of sample preparation. Five out of five individual hemolytic serum samples prepared by HLX14 or EU-Prolia met the criteria above. As a result, no hemolytic matrix effect is observed in 2% hemolytic serum samples.	Acceptable
Lipemic effect	The pooled serum samples had the %CV ≤ 25% and %bias within ± 25% which shows the viability of sample preparation. Five out of five individual lipemic serum samples prepared by HLX14 or EU-Prolia met the criteria above. As a result, no lipemic matrix effect is observed in hemolytic serum samples containing 501 mg/dL triglyceride.	Acceptable
Dilution linearity & hook effect	No hook effect observed at up to 98648.6 ng/mL of HLX14 or 98518.5 ng/mL of EU-Prolia, and no apparent dilution effect was observed up to 100-fold dilution.	Acceptable
Bench-top/process stability	HLX-14 and EU-Prolia: up to 72 hours at RT.	Acceptable
Freeze-Thaw stability	HLX-14 and EU-Prolia: up to 7 freeze-thaw cycles.	Acceptable
Long-term storage	HLX14 and EU-Prolia: Up to 354 days at -20±10℃ Up to 574 days at ≤ -60℃	Acceptable
Parallelism	The parallelism meets the acceptance criteria.	
Carry over	Not applicable.	
Method Performance in Study # HLX14-001 Part 2		

Assay passing rate	97.8% (179/183) • Total runs: 183 runs (including ISR runs) • Accepted runs: 179 Rejected runs: 3 Not performed: 1	Acceptable
Standard curve performance	• 1 (run 180) out of the 183 runs (0.55%) have %bias or %CV > 20.0 • Run 180 is for sample analysis & re-assay & ISR. This run has system suitability failed. There was no effect on sample analysis due to no valid data and has been rejected.	Acceptable
QC performance	• Cumulative bias (%bias): 3.6 to 6.8% • Cumulative precision (%CV): ≤ 8.8%	Acceptable
Method reproducibility	ISR was performed in 6.13 % (340/5551) of study samples and 99.1% (337/340) of samples met the pre-specified criteria	Acceptable
Study sample analysis/ stability	Samples were stored at -80°C. All samples analyzed within the established 574 days long-term stability (longest interval from collection to analysis:271 days).	Acceptable
Method Performance in Study # HLX14-3001		
Assay passing rate	95.0% (134/141) • Total runs: 141 (including ISR runs) • Accepted runs: 134 Rejected runs: 4 Analysis-terminated runs: 3	Acceptable
Standard curve performance	• Cumulative accuracy (%bias) from LLOQ to ULOQ: –0.3 to 1.3% • Cumulative precision (%CV) from LLOQ to ULOQ: ≤ 2.8%	Acceptable
QC performance	• Cumulative accuracy (%bias): 3.5 to 4.5 % • Cumulative precision (%CV): ≤ 15.5 %	Acceptable
Method reproducibility	• ISR was performed in 7.9% (269/4064) of study samples and 87.7% (236/269) of samples met the pre-specified criteria	Acceptable
Study sample analysis/ stability	• Samples were stored at -80°C. All samples analyzed within the established 574 days long-term stability (longest interval from collection to analysis:327 days).	Acceptable

**Concentration data from impacted samples removed for PK analysis*

Pharmacodynamics

CTX levels were determined in the HLX14-001 part I/II and HLX14-002-PMOP301 studies using the Roche Cobas 6000 e601 Immunoassay Analyzer. This assay follows the sandwich principle. Initially, the sample is incubated with a biotinylated monoclonal anti-CTX antibody to liberate the antigen from serum components. Subsequently, streptavidin-coated microparticles and a monoclonal CTX-specific antibody labeled with a ruthenium complex are added, forming a sandwich complex bound to the solid phase via biotin-streptavidin interaction. The reaction mixture is then aspirated into the measuring cell, where microparticles are magnetically captured onto the electrode surface. Unbound substances are removed. A voltage is applied to the electrode, inducing chemiluminescent emission measured by a photomultiplier. Results are determined via a calibration curve, generated by 2-point calibration and a master curve provided via the reagent barcode.

Levels of P1NP in the HLX14- 002-PMOP301 clinical study was measured using a validated ELISA assay. Firstly, the standard curve samples, QC samples and validation samples are added to the pre-coated multi-well microplate. After incubation and washing, the biotin-labeled detection antibody is added. Then streptavidin-HRP is added. After washing extra streptavidin-HRP, TMB is added to develop a soluble blue reaction that can be stopped with acid, forming a yellow reaction product which enables accurate intensity measurement at 450 nm and 630 nm.

These PD assays were considered fully validated with respect to precision, accuracy, hemolyzed/lipemic serum interference, parallelism, selectivity, dilution linearity, robustness, and tested for stability (short-term, long-term, freeze/thaw cycles).

13.3.2. Other Clinical Pharmacology Information

Not Applicable

13.4. Clinical Appendices

Table 48: Schedule of Assessments Study HLX14-002PMOP301

Table 9-3 Schedule of Activities

Study period	Screening period [1]	Treatment period													End-of-study visit [19]
		Treatment period 1										Treatment period 2			
Visits		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Week	W-4 to W-1	W0	W2	W4	W8	W13	W15	W19	W23	W26	W39	W52	W54	W65	W78
Day	D-28 to D-1	D1	D15	D29	D57	D92	D106	D134	D162	D183	D274	D365	D379	D456	D547
Time window (days)	0	0	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14
Informed Consent Form	X														
Inclusion/Exclusion criteria	X														
Dispensing subject ID card	X														
Demographics	X														
Medical history, fracture history, and medication history	X														
Smoking history	X														
Drinking history	X														
Height/Weight	X	X		X		X				X	X	X	X	X	X
Vital signs	X	X		X		X				X	X	X	X	X	X
Physical examinations	X	X		X		X				X	X	X	X	X	X
12-lead ECG [2]	X	X		X		X				X	X	X	X	X	X
Local laboratory tests															
Hematology [3]	X	X		X		X				X	X	X	X	X	X
Clinical Chemistry [4]	X	X		X		X				X	X	X	X	X	X

Study period	Screening period [1]	Treatment period													End-of-study visit [19]
		Treatment period 1										Treatment period 2			
Visits		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Week	W-4 to W-1	W0	W2	W4	W8	W13	W15	W19	W23	W26	W39	W52	W54	W65	W78
Day	D-28 to D-1	D1	D15	D29	D57	D92	D106	D134	D162	D183	D274	D365	D379	D456	D547
Time window (days)	0	0	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14
Urinalysis [5]	X	X		X		X				X	X	X	X	X	X
Coagulation [6]	X	X		X		X				X	X	X	X	X	X
25-OH vitamin D [7]	X	X		X		X				X	X	X	X	X	X
FSH [8] (optional)	X														
Virology test [9]	X														
Imaging examination															
X-ray[10]	X											X			X
DXA scan [11]	X									X		X			X
Study procedures															
HLX14/Prolia® administration [12]		X								X		X			
Calcium and vitamin D supplementation [13]	X	X													
Sample collection (central laboratory tests)															
s-CTX/s-P1NP sampling[14]		X	X	X	X	X	X	X	X	X	X	X			X
PK sampling [15]		X	X	X	X	X				X	X	X			X
ADA/NAb sampling [16]		X	X	X	X	X				X	X	X	X	X	X

Study period	Screening period [1]	Treatment period													End-of-study visit [19]
		Treatment period 1										Treatment period 2			
Visits		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Week	W-4 to W-1	W0	W2	W4	W8	W13	W15	W19	W23	W26	W39	W52	W54	W65	W78
Day	D-28 to D-1	D1	D15	D29	D57	D92	D106	D134	D162	D183	D274	D365	D379	D456	D547
Time window (days)	0	0	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14
Concomitant medications and adverse events															
Concomitant medications [17]	X														
Adverse events [18]	X														

Note: the letter "W" and "D" were standing for week and day, respectively.

[1] The screening period was 4 weeks. In this study, re-screening was allowed. In the case of ineligible laboratory parameters, re-test could be performed within the screening time window, and the finally confirmed screening failures needed to be recorded in the EDC system. Re-screening could be performed at the discretion of the Investigator, and a screening number needed to be re-assigned.

[2] 12-lead ECG: if a 12-lead ECG was performed within 7 days before the first dose, it could be used as the baseline and this item was not required to be repeated before the first dose.

[3] Hematology: if hematology test was performed within 7 days before the first dose, it could be used as the baseline and this item was not required to be repeated before the first dose. Hematology included red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, platelet count, neutrophil count, neutrophil percentage, lymphocyte count, lymphocyte percentage, eosinophil count, and basophil count.

[4] Clinical Chemistry: if clinical chemistry test was performed within 7 days before the first dose, it could be used as the baseline and this item was not required to be repeated before the first dose. Chemistry included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), direct bilirubin (DBil), indirect bilirubin (IBil), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total protein (TP), albumin (Alb), cholesterol (CHOL), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), blood urea nitrogen/urea (UREA), uric acid (UA), creatinine (Cr), fasting plasma glucose (Glu), phosphorus (P), potassium (K^+), sodium (Na^+), chlorine (Cl^-), calcium (Ca^{2+}), and magnesium (Mg).

[5] Urinalysis: if urinalysis was performed within 7 before the first dose, it could be used as the baseline and this item was not required to be repeated before the first dose. Urinalysis included pH, specific gravity, glucose, protein, urobilinogen, bilirubin, count of WBC in urine, ketone bodies, and count of RBC in urine. In V1, V9 and V11 administration visits, when hematology, chemistry and urinalysis and study drug administration were arranged on the same day, the study drug administration could only be arranged after the examination results were obtained.

[6] Coagulation function: if coagulation function test was performed within 7 days before the first dose, it could be used as the baseline and this item was not required to be repeated before the first dose. Coagulation function included thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen quantification (Fg), D-dimer (D-dimer) and international normalized ratio (INR).

[7] 25-OH vitamin D: To be retested after vitamin D supplementation was allowed. If 25-OH VD test was performed within 7 within before the first dose, it could be used as the baseline and this item was not required to be repeated before the first dose.

[8] FSH (optional): if a subject had unknown status of bilateral oophorectomy or had undergone hysterectomy but with the ovaries reserved, FSH test could be performed to confirm the post-operative menopausal status.

[9] Virology test: results within 28 days prior to initial dosing could be used as a baseline. Treponema pallidum antibodies, human immunodeficiency virus antibodies, HBsAg, HBsAb, HBeAg, HBeAb, HBcAb, and hepatitis C virus antibodies would be tested at screening period at study hospitals. If HBsAg was positive or HBcAb was positive, a quantitative HBV DNA test would need to be added; if HCV antibody was positive, a quantitative HCV RNA test would need to be added.

[10] X-ray: test results within 60 days prior to initial dosing could be used as baseline. X-rays included the vertebrae (lumbar vertebrae should be done, cervical, thoracic vertebrae and other parts of the vertebrae determined by the Investigator) and hip. If the subject had any signs of fracture during the study, X-ray test could be done to confirm (not limited to the two parts).

[11] DXA scan: results within 60 days prior to initial dosing could be used as a baseline (same hospital, same DXA device). DXA scan was performed at screening period, and at D183 (within 7 days before administration), D365 (within 7 days before administration), and D547 (end-of-study visit) visits. The examination sites included lumbar spine, total hip, and femoral neck. All images needed to be transmitted to central imaging.

[12] Dosing was done after the Investigator had completed the evaluation of laboratory results. The interval between the dates of randomization and administration of the study drugs did not exceed 3 days. Subcutaneous injection of 60 mg of the study drug (HLX14 or Prolia®) was administered on D1, D183 and D365 (±7 days).

[13] Calcium and vitamin D: calcium and vitamin D supplementation was allowed since the screening period. Calcium supplementation was not allowed within 24 h before blood calcium (biochemical) testing. Daily supplement with at least 1000 mg of calcium and at least 400 IU of vitamin D was continued after the first dose of study drug until end-of-study.

[14] s-CTX/s-P1NP blood sample collection: fasting blood samples would be collected before noon at D1 (within 7 days before the first dosing), D15, D29, D57, D92, D106, D134, D162, D183 (within 7 days before the second dosing), D274, D365 (within 7 days before the third dosing) and D547 (end-of-study visit) visits and sent to the central laboratory for testing. Fasting state was defined as nighttime fasting, and if nighttime fasting was not feasible, at least 8 h of fasting was required. The test results on D1 or after the baseline were obtained by the central laboratory rather than the individuals, where the test results on D1 (within 7 days before dosing) was used as baseline evaluation.

[15] PK blood sample collection: blood samples was collected at D1 (within 7 days before the first dosing), D15, D29, D57, D92, D183 (within 7 days before the second dosing), D274, D365 (within 7 days before the third dosing) and D547 (end-of-study visit) visits. If any AE suggestive of an immune reaction was detected outside of the pre-planned collection schedule, PK blood sample was collected whenever possible.

[16] ADA/NAb blood sample collection: blood samples were collected at D1 (within 7 days before the first dosing), D15, D29, D57, D92, D183 (within 7 days before the second dosing), D274, D365 (within 7 days before the third dosing), D379, D456 and D547 (end-of-study visit) visits; if a sample was ADA-positive, it was tested for NAb. If any AE suggestive of an immune reaction was detected outside of the pre-planned collection schedule, ADA blood sample was collected whenever possible.

[17] Concomitant medications: concomitant medications were recorded from the time of signing the ICF until end-of-study.

[18] AEs: AEs were recorded from the time of ICF signing until end-of-study. If the Investigator learned of any treatment-related SAE in a subject after she had completed follow-up or withdrawn from the study, it was reported to the Sponsor in a timely manner.

[19] End-of-study visit: D547 (±14 days) or subjects who withdrew from the study early should complete the end-of-study visit within 7 days of their decision to withdraw. Relevant tests that had been done in the past 14 days might not be repeated. If the interval between the DXA scan/X-ray and the previous examination was less than 90 days, the DXA/X-ray scan did not need to be repeated.

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Entry Criteria in Study HLX14-002PMOP301

Subjects who met all the following criteria were allowed to be enrolled:

Inclusion Criteria:

1. Subjects voluntarily signed the ICF, understood the nature, objectives, and procedures of the study, and were willing to comply with the procedures during the study.
2. Ambulatory postmenopausal women with osteoporosis aged 60-90 years (both inclusive).
3. Postmenopausal, defined as > 2 years of menopause, i.e., > 2 years of spontaneous amenorrhea or > 2 years after bilateral oophorectomy. If a subject had unknown status of bilateral oophorectomy or had undergone hysterectomy but with the ovaries reserved, follicular stimulating hormone (FSH) level > 40 U/L could be used to confirm the post-operative menopausal status
4. Bone mineral density (BMD) T-score between −2.5 and −4.0 at the lumbar spine or total hip, i.e., −4.0 < T-score ≤ −2.5, as assessed by the central imaging at the time of screening, based on dual-energy X-ray absorptiometry (DXA) scans.
5. At least 2 vertebrae in the L1-L4 region of lumbar spine and at least one hip were evaluable by DXA, assessed by the central imaging.

Subjects who met any of the following criteria were not allowed to be enrolled:

Exclusion Criteria:

1. Diseases that might affect bone metabolism: various metabolic bone diseases, such as osteomalacia or osteogenesis imperfecta; Paget's disease (Paget disease of bone); Cushing's syndrome; hyperprolactinemia; hypopituitarism; acromegaly; multiple myeloma; hyperparathyroidism or hypoparathyroidism.
2. Thyroid disorders: hyperthyroidism or hypothyroidism; only subjects with hypothyroidism receiving stable thyroid hormone replacement therapy might be included, according to the following criteria:
    i. If thyroid stimulating hormone (TSH) level was below local normal range, subject was not eligible for the study;
    ii. If TSH level increased (> 5.5 μIU/mL but ≤ 10.0 μIU/mL), meanwhile serum thyroxine free (FT4) was within the normal range, subject was eligible. If serum FT4 was not within normal range, subject was not eligible for the study;
    iii. If TSH level was > 10.0 μIU/mL, subject was not eligible for the study.
3. Rheumatoid arthritis or ankylosing spondylitis.
4. Malignancies: active malignancies (except fully resected cutaneous basal cell or squamous cell carcinoma, cervical cancer or breast ductal carcinoma in situ) within the last 5 years prior to signing the ICF.
5. Malabsorption syndrome or various gastrointestinal disorders associated with malabsorption, e.g., Crohn's disease and chronic pancreatitis, and subjects with known malabsorption of calcium or vitamin D.

6. Severe renal impairment due to renal disease with a glomerular filtration rate < 30 mL/min (recommended to calculate as per Cockcroft-Gault (CG) formula provided in Appendix 16.1.1 V5.0 protocol Appendix 5).
7. Hepatic diseases:
    i. Liver cirrhosis;
    ii. Unstable liver disease (as defined by the presence of ascites, hepatic encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices or persistent jaundice);
    iii. Known or Investigator-determined clinically significant biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones and gallbladder polyps);
    iv. Subjects positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) test must undergo the hepatitis B virus deoxyribonucleic acid (HBV DNA) titer test (excluded if HBV DNA > 1000 cps/mL or 200 IU/mL), and subjects positive for hepatitis C virus (HCV) antibody must undergo the hepatitis C virus ribonucleic acid (HCV RNA) test (excluded if HCV RNA was positive);
    v. Severe hepatic insufficiency: Serum aspartate aminotransferase (AST) ≥ 2 × upper limit of normal (ULN); serum alanine aminotransferase (ALT) ≥ 2 × ULN; bilirubin ≥ 1.5 × ULN (when direct bilirubin was < 35% total bilirubin, indirect bilirubin ≥ 1.5 × ULN was allowed).
8. With serious primary diseases in the cardiovascular, cerebrovascular, or hematopoietic system judged by the Investigator.
9. Positive for human immunodeficiency virus (HIV) antibody.
10. Vitamin D deficiency: defined as 25-(OH) vitamin D level < 20 ng/mL. Subjects were allowed to be re-tested for 25-(OH) vitamin D level after vitamin D repletion.
11. Abnormal serum calcium: current hypocalcaemia or hypercalcemia, defined as that albumin-adjusted serum calcium level was not within the normal limit (hypoproteinemia serum calcium correction formula, as detailed in Appendix 16.1.1 V5.0 protocol Appendix 6). Subjects must not receive calcium supplements within 24 h before blood drawing for serum calcium screening.
12. Oral and dental diseases: prior or present evidence of osteomyelitis or osteonecrosis of the jaw; acute dental or jaw disease requiring oral surgery; planned invasive dental procedures; non-healed dental or oral surgery.
13. Active or uncontrolled infection requiring systemic therapy within 2 weeks prior to first dose.
14. Type 1 diabetic patients, or type 2 diabetic patients who had poor blood glucose control or were treated with insulin, glucagon-like peptide-1 (GLP-1), thiazolidinediones, SGLT2 inhibitors, etc.
15. Participating in clinical trials of other medical devices or drugs or within 30 days or 5 half-lives after the last visit in the clinical trials of other medical devices or drugs (non-bone metabolism related drugs) (whichever was longer, started from the date of ICF signing).
16. Bone metabolism related drugs should comply with the corresponding prohibition time limit, and anti-osteoporosis drugs should be excluded. Those who had failed

in the screening period of other clinical trials but had not yet been treated with other drugs/clinical devices could be included in this study.

17. Had received denosumab and its biosimilars, or romosozumab and its biosimilars, or cathepsin K inhibitor therapy prior to randomization.
18. Had received the following osteoporosis treatments, or medications that affected bone metabolism or any herbal medications:
    i. Use of bisphosphonates (oral or intravenous), fluoride and strontium prior to randomization;
    ii. Use of parathyroid hormone (PTH) or PTH analogues, such as teriparatide, within 12 months prior to randomization;
    iii. Use of systemic hormone replacement therapy (HRT), selective estrogen receptor modulators, tibolone, anabolic hormones, testosterone, androgens, gonadotropin releasing hormone agonists, or adrenocorticotropic hormone, within 12 months prior to randomization;
    iv. Use of calcitonin, calcitriol, alfacalcidol or vitamin D analogues within 12 months prior to randomization;
    v. Use of any of the following within 3 months prior to randomization: heparin, warfarin, anticonvulsants (except benzodiazepines), systemic use of ketoconazole, cinacalcet, aluminum, lithium, protease inhibitors, methotrexate, and oral or parenteral glucocorticoids (≥ 5 mg/day prednisone daily or equivalent for > 10 days);
    vi. Use of any herbal medications within 2 weeks (if the herbal medications contained the above components that affected bone metabolism, the corresponding elution process of bone metabolism components should be followed).

Table 49: Prohibited Concomitant Medications and Duration of Prohibition Prior to Study Drug Administration

Medications	Period prohibited prior to randomization
• Oral or intravenous bisphosphonates • Fluorides • Strontium	Excluded
• Parathyroid hormone or PTH analogues • Systemic hormone replacement therapy • Selective estrogen receptor modulators • Tibolone • Anabolic hormones • Testosterone • Androgens • Gonadotropin releasing hormone agonists • Adrenocorticotropic hormone • Calcitonin	Within 12 months

• Calcitriol, alfacalcidol and vitamin D analogues	
• Heparin, warfarin • Anticonvulsants (except benzodiazepines) • Systemic use of ketoconazole • Cinacalcet • Aluminum • Lithium • Protease inhibitors • Methotrexate • Oral or parenteral glucocorticoids (≥ 5 mg/day prednisone daily or equivalent for > 10 days)	Within 3 months
• Herbal medications (if the herbal medications contained the above components that affected bone metabolism, should follow the corresponding elution period of bone metabolism components)	Within 2 weeks

19. Subjects with a history or presence of hip fracture or prevalent vertebral fracture (any severe or more than 2 moderate prevalent vertebral fractures).
20. Presence of active healing fracture in the opinion of the Investigator.
21. Subjects at very high risk of fracture who must be treated immediately with an active drug in the opinion of the Investigator.
22. Known allergic to the drugs listed in the study protocol, including a history of allergy to denosumab, any recombinant protein drugs, or any ingredients used in HLX14 or Prolia
23. With a history and presence of smoking, except for the following situation:
    i. Non-smokers (a history of never smoking > 5 cigarettes/day and not smoking at all
    ii. for at least the last 2 years prior to screening process);
    iii. Light smokers (with smoking habit < 5 cigarettes/day, smoking period < 10 years).
    iv. Light smokers should have not smoked more than 1 cigarette in the week before starting the medical screening process.
24. With a history of drug or alcohol abuse, and with evidence of alcohol or drug abuse within 12 months.
25. Various physical or psychiatric disorders or laboratory abnormalities which, in the opinion of the Investigator, would prevent the subject from following the study procedures and completing the study, or interfere with the interpretation of study results.
26. Or subjects who had other conditions rendering them unsuitable for inclusion as judged by the Investigator.

Source: Clinical Study Report Version 2.0 Section 9.3 page 51-55

Table 50: Study Objectives and Endpoints

Objectives	Endpoints
Primary (Co-Primary)	
• To assess the equivalence of the primary clinical efficacy endpoint between HLX14 and comparator Prolia® in postmenopausal women with osteoporosis at high risk of fracture. • To assess the equivalence of the primary PD endpoint between HLX14 and comparator Prolia® in postmenopausal women with osteoporosis at high risk of fracture.	• Percent change from baseline in BMD at the lumbar spine to Week 52 (assessed by the central imaging). Note: the percent change in BMD was calculated as: (test value - baseline value)/(baseline value) × 100% • Area under the effect-time curve for percent change of serum type I collagen C-telopeptide (s-CTX) from baseline to Week 26 ($AUEC_{0-26W}$).
Secondary	
• To assess the equivalence of secondary clinical efficacy endpoints between HLX14 and comparator Prolia® in postmenopausal women with osteoporosis at high risk of fracture. • To assess the equivalence of secondary PD endpoints between HLX14 and comparator Prolia® in postmenopausal women with osteoporosis at high risk of fracture.	• Percent changes from baseline in BMD at the lumbar spine to Week 26, Week 52, Week78 (assessed by Investigator). • Fracture rate from baseline to Week 52, Week 78. • Percent changes in BMD at lumbar spine from baseline to Week 26, Week 78 (assessed by the central imaging). • Percent changes in BMD at total hip from baseline to Week 26, Week 52 and Week 78 (assessed by the central imaging and Investigator). • Percent changes in BMD at the femoral neck from baseline to Week 26, Week 52 and Week 78 (assessed by the central imaging and Investigator). Note: fracture rate = (number of subjects with new fractures/total number of subjects) × 100% The percent change in BMD was calculated as: (test value - baseline value)/(baseline value) × 100% • Relative percent changes in s-CTX from baseline to D15, D29, D57, D92, D106, D134, D162, D183 (within 7 days prior to the second dose), D274, D365 (within 7 days prior to the third dose) and D547 (at the end-of-study visit). • Relative percent changes in serum procollagen type I N propeptide (s-P1NP) from baseline to D15, D29, D57, D92, D106, D134, D162, D183 (within 7 days prior to the second dose), D274, D365 (within 7 days prior to the third dose), and D547 (at the end-of-study visit).

	The relative percent change was calculated as: (test value at time points evaluated-baseline value)/(baseline value) × 100%
Others	
Rate of intercurrent events • To compare the intercurrent events (ICEs) rate of HLX14 and comparator Prolia® in postmenopausal women with osteoporosis at high risk of fracture. Safety • To compare the safety of HLX14 and comparator Prolia® in postmenopausal women with osteoporosis at high risk of fracture. Pharmacokinetics • To compare the PK of HLX14 and comparator Prolia® in postmenopausal women with osteoporosis at high risk of fracture. Immunogenicity • To compare the immunogenicity of HLX14 and comparator Prolia® in postmenopausal women with osteoporosis at high risk of fracture.	Intercurrent events • Premature treatment discontinuation: 1) Treatment discontinuation due to adverse event (AE) (related to treatment); 2) Treatment discontinuation due to lack of efficacy (related to treatment); 3) Treatment discontinuation for other reasons (not related to treatment). • Bone-affecting interventions: 1) Use of prohibited drugs (were confirmed in data review meeting); 2) Non-drug intervention (including but not limited to bilateral oophorectomy). • AE's affecting bone: 1) Injury, poisoning and procedural complications: spinal fracture, hip fracture and so on; 2) Metabolism and nutrition disorders/endocrine disorders: diabetes mellitus (new-onset), hyperthyroidism and so on; 3) Gastrointestinal disorders: Crohn's disease, ulcerative colitis and so on; 4) Musculoskeletal and connective tissue disorders: rheumatoid arthritis, ankylosing spondylitis and so on; 5) Nervous system disorders: Parkinson's disease, spinal cord injury and so on; 6) Other: chronic obstructive pulmonary disease, HIV infection and so on. • Changes in concomitant medication: thiazolidinedione, GLP-1 receptor agonists and so on (were confirmed in data review meeting). • Other events that could impact the concentration of s-CTX and s-P1NP: such as missing sampling, sample hemolysis, abnormal data and so on at some important concentration points. Safety • Incidences of AEs and SAEs, laboratory tests (routine blood test, blood biochemistry, urinalysis, etc.), 12-lead electrocardiogram (ECG), physical examinations, vital signs, etc. Pharmacokinetics • Serum concentrations of the study drugs (HLX14 and comparator Prolia®) at each time point. Immunogenicity • Positive rates of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) to the study drugs.

Source: Clinical Study Report Version 2.0 Section 9 page 48-49

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/s/

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