24 July 2025
EMA/CHMP/228042/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bilprevda

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/006435/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC0-inf	Area under the Serum Drug Concentration-time Curve from Time 0 to Infinity (inf) following Administration
AUC0-t	Area under the Serum Drug Concentration-time Curve from Time 0 to the Last Concentration-quantifiable Time t
AUEC0-t	Area under the Effect-time Curve from Time 0 to Last Time of Quantifiable Concentration of s-CTX
BMD	Bone Mineral Density
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cmax	Maximum Serum Drug Concentration
CN	China
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiography
EMA	European Medicines Agency
EU	European Union
ICEs	Intercurrent Events
IgG2	Immunoglobulin G 2
Imax	Maximum Percent Inhibition of s-CTX
Imin	Minimum Observed Concentration of s-CTX
ITT	Intention-to-treat
LS	Least Squares
NIH	National Institutes of Health
OPG	Osteoprotegerin
PD	Pharmacodynamic
PDPS	PD Parameter Set
PDS	Pharmacodynamic Set
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
PMOP	Post-menopausal Osteoporosis
PPS	Per Protocol Set
PT	Preferred Term
ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC0-inf	Area under the Serum Drug Concentration-time Curve from Time 0 to Infinity (inf) following Administration
AUC0-t	Area under the Serum Drug Concentration-time Curve from Time 0 to the Last Concentration-quantifiable Time t
AUEC0-t	Area under the Effect-time Curve from Time 0 to Last Time of Quantifiable Concentration of s-CTX
BMD	Bone Mineral Density
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cmax	Maximum Serum Drug Concentration
CN	China
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiography
EMA	European Medicines Agency
EU	European Union
ICEs	Intercurrent Events
IgG2	Immunoglobulin G 2
Imax	Maximum Percent Inhibition of s-CTX
Imin	Minimum Observed Concentration of s-CTX
ITT	Intention-to-treat
LS	Least Squares
NIH	National Institutes of Health

OPG	Osteoprotegerin
PD	Pharmacodynamic
PDPS	PD Parameter Set
PDS	Pharmacodynamic Set
RANKL	Receptor Activator of Nuclear Factor-κB Ligand
s-CTX	Serum C-terminal Telopeptide of Type I Collagen
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
s-P1NP	Serum Procollagen Type I N Propeptide
SS	Safety Set
t1/2	Elimination Half Life
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
Tmax	Time to Reach Maximum Serum Drug Concentration
Tmin	Time to Reach Minimum s-CTX Concentration
TRAE	Treatment-related AE

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Henlius Europe GmbH submitted on 30 April 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Bilprevda, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

- Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone (see section 5.1).

- Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal product.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

This application is submitted as a multiple of Bildyos simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Xgeva 120 mg solution for injection
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 13-07-2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/703

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Xgeva 120 mg solution for injection
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 13-07-2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/703

Medicinal product which is or has been authorised in accordance with Union provisions in force and to

which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Xgeva 120 mg solution for injection in vial
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 13-07-2011
- Marketing authorisation granted by:
  - Union

  Marketing authorisation number(s): EU/1/11/703

1.3. Information on paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 June 2022	EMA/SA/0000084242	Linda Trauffler, Sif Ormarsdóttir
13 October 2022	EMA/SA/0000099806	Linda Trauffler, Juha Kolehmainen

The scientific advice pertained to the following quality and clinical aspects:

- Analytical similarity study strategy, including overall study design rationale, analytical testing panel, sample lot selection, analytical methods, and statistical approach.

- Design of a Phase I pharmacokinetics (PK) comparative two-part study in healthy male volunteers in China; Part 1: a randomized, parallel-group pilot study of single dose HLX14-P vs. EU-sourced Prolia; Part 2: a single-dose, four-arm parallel study of HLX14-P, EU-sourced Prolia, China-sourced Prolia, and US-sourced Prolia; including dose selection, study population, selection criteria, primary and secondary endpoints, sample size, statistical approach, PK and immunogenicity testing strategy.

- Design of a randomized, double-blind, international multi-center Phase III study in postmenopausal women with osteoporosis at high risk of fracture to evaluate the pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity of HLX14-P versus Prolia (EU-sourced Prolia and China-sourced Prolia) including choice of indication, dose, dosing interval criteria for HLX14-P, study population, primary and secondary endpoints, choice of

comparator products, stratification factors, treatment duration, intercurrent events and strategy with estimand framework, sample size, statistical approach.

- Extrapolation of clinical study results to all approved indications.
- Exclusion of attributes from the analytical similarity assessment, lots to be included in the analytical similarity study and data pooling for certain attributes; similarity assessment criteria.
- Revised phase I study design, phase III study design aspects including study population, estimand framework and analysis plan.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christian Gartner Co-Rapporteur: Tomas Radimersky

The application was received by the EMA on	30 April 2024
The procedure started on	23 May 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 August 2024
The CHMP Co-Rapporteur's Critique was circulated to all CHMP and PRAC members on	17 August 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 August 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 December 2024
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at one drug substance manufacturing and testing site in China, and one drug product manufacturing site in China, between 26 March to 02 April 2025. The outcome of the inspection carried out was issued on	16 June 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	04 February 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2025
The CHMP agreed on a list of outstanding issues to be sent to the	27 February 2025

applicant on	
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 June 2025
The CHMP Rapporteurs circulated the preliminary CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	09 July 2025
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	17 July 2025
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Bilprevda on	24 July 2025

2. Scientific discussion

2.1. About the product

Bilprevda (HLX14) was developed as a biosimilar for Xgeva (INN: denosumab), and was developed with the same strength and presentation:

- Xgeva: 120 mg/1.7mL single use vial

The applicant is claiming all the approved indications for the reference product Xgeva.

Denosumab is a human monoclonal IgG2 type antibody that binds to RANKL (Receptor activator of nuclear factor kappa-B ligand) with high affinity and specificity, inhibiting the interaction of RANKL with RANK on the osteoclast membrane. This inhibition leads to the suppression of RANKL/RANK-mediated differentiation, maturation, and activation of osteoclasts, ultimately reducing bone resorption and the incidence of skeletal-related adverse events. The mechanism of action of denosumab is identical across the different approved indications.

2.2. Type of Application and aspects on development

Bilprevda (HLX14) is a proposed biosimilar to EU-Xgeva.

The applicant developed three presentations of HLX14; Bildyos (HLX14) 60 mg/mL in vials and HLX14 60 mg in pre-filled syringes were developed as a proposed biosimilar to Prolia, Bilprevda (HLX14) 120 mg (70 mg/mL) in vials was developed as a proposed biosimilar to Xgeva. The proposed indications for both Bildyos and Bilprevda are the same as those of the reference drugs Prolia and Xgeva, respectively.

The development has been conducted in line with EMA guidance documents for biosimilars. A comprehensive analytical comparability study according to EMA/CHMP/BWP/247713/2012 has been performed supporting the biosimilarity claim.

During the development of HLX14, the applicant sought Scientific Advice (SA) from the EMA Scientific Advice Working Party. The SA was requested to discuss the quality and clinical development of HLX14.

Extensive analytical similarity studies have been performed against the reference product, Prolia and Xgeva, and clinical studies have been performed against the reference product, Prolia.

The clinical programme consists of two clinical studies:

- a Phase I study (HLX14-001) and a Phase III study (HLX14-002-PMOP301).

The Phase I study, conducted in healthy adult males, was designed to assess the pharmacokinetic, pharmacodynamic, safety, tolerability, and immunogenicity of HLX14 (60 mg, vial) versus US-Prolia, EU-Prolia, and China (CN)-Prolia. The Phase III study, conducted in postmenopausal women with osteoporosis at high risk of fracture, assessed the efficacy, PK, PD, safety, tolerability, and immunogenicity of HLX14 (60 mg, vial) versus EU-Prolia.

The extrapolation to the approved XGEVA indications is supported by the identical mechanism of action of denosumab across all approved indications (for the reference products Prolia and Xgeva).

2.3. Quality aspects

2.3.1. Introduction

The finished product (FP) Bilprevda is presented as a sterile, clear to slightly opalescent, colourless to slightly yellow solution for injection, containing 70 mg of denosumab as active substance (AS) in 1 mL of solution (70 mg/mL). Other ingredients are acetic acid glacial, sodium hydroxide (for pH adjustment), sorbitol (E420), polysorbate 20 and water for injections.

The FP is packaged in a 2 mL single use borosilicate vial (type I glass) with bromobutyl rubber stopper, and sealed with an aluminium-plastic combination caps.

2.3.2. Active substance

2.3.2.1. General information

Denosumab (HLX14) is an anti-RANKL fully human IgG2 kappa monoclonal antibody, produced using recombinant Chinese Hamster Ovary (CHO) cell culture technology. HLX14 is a glycosylated monoclonal antibody consisting of 2 identical heavy chains and 2 identical light chains covalently linked by disulfide bonds. Each heavy chain has 448 amino acids, while each light chain has 215 amino acids. The entire antibody contains 6 pairs of interchain disulfide bonds and 12 pairs of intrachain disulfide bonds. Each heavy chain contains 1 N-glycosylation site (N298). The AS amino acid sequence is meant to be the same as for denosumab in the reference medicinal product. Denosumab AS is a monomeric IgG2 monoclonal antibody and includes a mixture of three disulphide isoforms A, A/B and B. Structure and properties of denosumab are sufficiently described.

2.3.2.2. Manufacture, characterisation and process controls

The active substance is manufactured at Shanghai Henlius Biologics Co. Ltd. Building 1, No 182 Wenjun Road, Songjiang, Shanghai, 201616, China. During the assessment, a Major Objection (MO) was raised,

requesting confirmation of GMP compliance to all listed activities of the AS manufacturer. Confirmation was received and a valid EMA GMP certificate is available. The MO was considered solved.

All sites involved in manufacture and control of the active substance operate in accordance with EU GMP.

Description of manufacturing process and process controls

A brief overview of the AS manufacturing process is provided, followed by a detailed description of each process unit operation. The AS manufacturing process is a standard process which is divided into an upstream and downstream process. The AS is manufactured by single-use technologies using CHO cells.

The manufacturing process begins with thawing of a Working Cell Bank (WCB) vial that is subsequently expanded in shake flasks and seed bioreactors, to reach a final fed batch production bioreactor. The total duration of cell culture from WCB vial thaw until harvest is controlled. The bioreactor culture is harvested, clarified and purified with column chromatography steps, orthogonal virus clearance steps. Subsequently, an Ultrafiltration/Diafiltration unit operation is used for AS concentration and buffer exchange. All the excipients are added, and concentrations are adjusted to match the final AS. The formulated AS is filtered, filled into storage bags, and stored at the controlled condition.

The AS is composed of HLX14, glacial acetic acid, sorbitol, polysorbate, and pH adjusted with appropriate amount of sodium hydroxide. The process description is considered adequate.

A Major Objection on the process control strategy was raised. As response to the MO raised, the applicant confirmed that a quality risk management has been applied to identify the risks associated with source and process variables and to mitigate the overall manufacturing risks. The applicant also outlined that adherence to the ICH guidelines (ICH Q8, ICH Q9) on process design, process validation and continued process verification is aimed. The applicant outlined that a risk assessment has been conducted based on existing knowledge of the impact of process parameters on unit process performance, as well as on the final product's quality, safety, and efficacy. Certain process parameters are identified as critical process parameters based on their known impact on safety and efficacy. Other process parameters that could affect process performance were identified and subjected to further process characterization. Three types of process characterization (PC) study experiments were employed as appropriate, including design of experiments (DoE), one factor at a time study (OFAT) and extreme case study. Based on results of these experiments, the applicant established the impact of the parameters (within the studied range) on the Critical quality attributes (CQAs). The outlined strategy is agreed, and it was sufficiently clarified how process parameters were assigned as critical or non-critical.

The applicant clarifies that a tiered in-process control strategy has been adopted, which includes critical in-process controls (cIPCs), in-process controls (IPCs), as well as in-process tests (IPTs). The applicant indicates that any confirmed failure to meet predefined acceptance leads to batch rejection whereas in case of (non-critical) in-process controls the disposition of the batch is subjected to root cause analysis and impact analysis. As requested, a detailed explanation of the deviation management for critical and non-critical process steps has been provided and information updated accordingly. Reprocessing will be validated at commercial production scale when the condition is triggered. Acceptance criteria for process parameters and quality attributes for validation of reprocessing at commercial scale are included in the dossier. This strategy is in line with the EMA Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission, EMA/CHMP/BWP/187338/2014 and thus acceptable.

With the information provided, the MO on the control of the AS manufacturing process was considered solved and the active substance manufacturing process is considered acceptable.

Control of materials

The section on Control of Materials is appropriately addressed. Sufficient information on raw materials used in the AS manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. The use of each listed raw material in the manufacturing process is indicated. Qualitative composition of media is declared and a confirmation that an agreement is in place with the supplier to notify the MAH in case of changes to the medium is included. The host cell line for HLX14 is CHO cells. The cell bank system comprised of a Master Cell Bank (MCB) and WCB was sufficiently described. The characterisation of MCB and WCB was performed as per ICH Q5A and ICH Q5D. All characterisation testing results of MCB and WCB are listed in the dossier and met their corresponding acceptance criteria. MCB and WCB were confirmed to be free of adventitious agents and retroviruses. Cell substrate stability was confirmed and Limit of in Vitro Cell Age (LIVCA) was studied.

The characterisation and biosafety testing of End of production cells (EoPC) was performed as per ICH Q5A and WHO/FDA guidance. Additionally, testing of EOPC (derived from PPQ batch manufactured at 2000 L commercial scale) was conducted. Satisfactory summaries of the non-compendial methods for detection of adventitious agents have been provided. Storage stability protocols for MCB and WCB are presented. Finally, a protocol for the production and release of future, new working cell banks is included and is considered adequate.

Control of critical steps and intermediates

The section on Control of Critical Steps and Intermediates provides tabulated summaries of CPPs together with their PARs. Also, a summary of the IPC with their acceptance criteria is included.

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

Process validation

In the Process Validation section, the performed AS process performance qualification (PPQ) is described. Process performance qualification included consecutive upstream cell culture process runs from independent Working Cell Bank (vials) and consecutive downstream purification runs All the executive results for the consecutive PPQ batches met the corresponding acceptance criteria, with comparable quality and process performance. Therefore, it can be agreed that the proposed manufacturing process is reliable to produce target quality AS in a robust and reproducible manner.

Additional validation studies included hold time studies for process short-time intermediates, in-process microbial monitoring, resin and membrane lifetime studies, validation of the reprocessing and the shipping validation.

In summary, the validation results confirmed the stated maximum hold times of the short-time process intermediates. The in-process microbial monitoring plan (bioburden and bacterial endotoxin) are discussed. The applied filters are suitable for use under the defined manufacturing conditions. Lifetime studies of reusable resins were carried out with small-scale models which were qualified in downstream process characterisation. The actual lifetime will be determined based on the concurrent qualification results from three executions of UF/DF membranes qualification at commercial scale. Resin and membrane lifetime is executed on at-scale batches, as a concurrent validation exercise.

Reprocessing in designated approach is considered acceptable and will be triggered concurrently at commercial production scale. Acceptance criteria for process parameters and quality attributes for validation of reprocessing at commercial scale are included in the dossier. The strategy is in line with the

EMA Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission, EMA/CHMP/BWP/187338/2014 and thus acceptable.

A risk assessment for the single-use materials according to EMA/CHMP/BWP/187338/2014 has been included in the dossier. The risk associated with the extracts produced by the single-use components used in the manufacturing process is negligible.

A brief AS transport validation to the FP manufacturer is included and proved that the container protected the AS packaging integrity and kept the temperature within the temperature specified conditions.

The active substance manufacturing process has been validated adequately. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces denosumab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

Three different process versions have been described. A tabulated overview of the process changes together with a rationale for each process change has been presented. To address the implemented changes two comparability exercises have been conducted.

Since AS from the development process was used for the (PK) trials, an unambiguous and robust demonstration of comparability of clinical with commercial material was expected. However, comparability data to support change in AS from the clinical process and commercial process did not allow for a firm conclusion that AS materials from clinical and commercial processes are comparable and a Major Objection was raised. The basis to set comparability acceptance criteria for comparability study has been elaborated and raises no concerns. A summary of the selected statistical assessment methods for QAs is provided. The slight difference in quality attributes between the clinical process and commercial process have been discussed and justified in terms of their impact on the product's safety and efficacy. The justification provided can be accepted. Data from IgG2 isoforms, N- and C- terminal integrity, molecular mass, disulfide bridges linkage by peptide mapping in non-reduced conditions analysis is either provided. All analytical methods were either validated or qualified for the intended use. Validation and qualification data is included. The applicant provided additional stressed and forced degradation data for the clinical process and commercial process. Comparable degradation trend is concluded. Process parameters and in process monitoring results applied during the clinical process and commercial process are compared and they support scale change. In summary, comparability of clinical with commercial material is demonstrated and the Major Objection is considered solved.

Characterisation

The quality target product profile (QTPP) was generated based on the expectations on efficacy and safety of the product. Critical quality attributes for individual unit operations were selected for initial risk assessment of process parameter to identify those that may have significant impacts on CQAs. Scale down model for process characterisation studies were qualified to make sure it can be used to represent the process performance at manufacture scale. Raised uncertainties on the representativeness of the small-scale models for the commercial scale could be ruled out. Subsequently process characterisation study for each unit operation was carried out with univariate (e.g. OFAT) or multivariate studies (e.g. DoE) as appropriate using scale-down models to establish parameter-attribute relationships, and to identify the PARs. Finally based on the results of process characterisation studies, process parameters were further classified based on their potential impact on CQAs, as CPP and non-CPP by applying the

decision logic. Initially raised gaps which were included in the MO on the process control strategy are considered solved.

Elucidation of structure and other characteristics

Three AS batches generated with the intended commercial manufacturing process were used for elucidation of structural and functional characteristics.

Characterisation of the primary structure included amino acid sequence, molecular weight, disulfide linkage, IgG2 disulfide isoforms analysis, free thiols, and post-translational modifications. The amino acid sequence of three AS batches was consistent with the theoretical amino acid sequence of denosumab. The resulting molecular weights numerically matched the corresponding theoretical values within the expected variability of the methods. All disulfide bonds of the three theoretical IgG2 disulfide bond isomers could be confirmed. The results indicated that the disulfide linkages of three HLX14 AS batches were identical to the theoretical prediction with IgG2-A, IgG2-B and IgG2-A/B types. The quantitative results of IgG2 disulfide isoforms were presented, the same disulfide isoforms species and similar abundance distribution were detected.

Secondary and tertiary structure was studied, and resulting data showed comparable secondary and tertiary protein structures.

Charge variants including acidic peaks, main peak, and basic peaks were studied. Glycosylation included confirmation of the glycosylation site, N-glycan profiling, and quantification of sialic acids. Size variants including high-molecular-weight species, monomers, HC+LC, and NGHC were studied.

Protein content was measured by ultraviolet-visible spectrophotometer at 280 nm whereas general properties included pH, isoelectric point and osmolality.

Biological properties were studied by soluble RANKL binding and binding kinetics to soluble RANKL. In addition, cell-based assays involving Fab region of the antibody and the Fc effector function have been performed. Whereas the binding and Fab specific cell-based assays confirmed the activity of HLX14, absence of ADCC and CDC activity was demonstrated, showing that Fc effector functions do not play a role in the mode of action.

Characterisation of the immunological properties included binding assays for FcγRIa, FcγRIIa-R, FcγRIIa-H, FcγRIIb/c, FcγRIIIa-V, FcγRIIIa-F, FcγRIIIb, FcRn, and C1q. The results are in accordance with the nature of an IgG2 subtype.

The results demonstrated that the denosumab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of an IgG2-type antibody. In summary, the characterization is considered appropriate for this type of molecule.

Impurities

A brief discussion on the impurities has been provided. Sufficient batch data are provided which confirm that the purification process is capable of removing the process-related impurities. Product-related impurities have been comprehensively identified and characterized. Their potential biological activities and safety implications are thoroughly discussed.

In summary, a sufficient discussion on impurities is included.

2.3.2.3. Specification

The release and stability specifications for AS are comprised of a sound panel of standard and state-of-the-art methods addressing relevant quality attributes (identity, appearance, protein content, potency, purity, impurities and safety)

Justification of specification

The applicant has outlined their strategy for setting of release and stability acceptance criteria. For quantitative testing items without compendial requirement and relevant development data, an appropriate approach was used.

Analytical procedures

The analytical procedures are sufficiently described. Certain standard methods such as appearance by clarity and colour, pH, osmolality, protein content, bacterial endotoxins and bioburden are conducted according to Ph. Eur. For the in-house methods a brief method description including the method principle, required reagents and instruments, sample preparation, procedure, analysis, system suitability criteria and data reporting is included.

In-house methods were validated according to ICH Q2 whereas pharmacopeial methods were verified. A brief, tabulated summary of the validation results as well as a more detailed description of the conducted method validation is included. The validation performed confirms that the methods in place for release and stability testing are suitable for their intended use.

AS and FP are tested for endotoxin using the compendial LAL test based on the Limulus Amebocyte lysate. The applicant is informed that the Ph. Eur. recently adopted general text 2.6.32 on recombinant Factor C for Endotoxin control. Following ICH Q10, the applicant confirmed that the method development for bacterial endotoxins using recombinant factor C is ongoing and outlines the transition process.

Batch analysis

The batch analysis includes the batch release data from PPQ process and commercial process batches, clinical process as well as early process batches. These batches were tested according to the test methods and specifications applicable at the time of the testing and release. The batches complied with the specifications at the time of release. Considering the number of AS batches manufactured up to date, it can be concluded that the applicant has gained a considerable process and product knowledge. In summary, the batch analysis data available confirms the consistency of the manufacturing process.

Reference materials

A brief, but sufficient description of these reference standards and their characterisation is included.

The applicant briefly outlines the strategy on replacement of future reference standards in case the current primary reference standard or working reference standard depletes. Regarding the potency assignment of future reference standards, the applicant has elaborated on the potency requalification requirement of future reference standards. The defined acceptance criteria and number of tests are considered sufficient to avoid a potential drift in potency to future reference standards and hence is accepted. In addition, the risk of drifting can be mitigated by implementing a two-tiered system for

reference standards. The applicant confirmed that the primary reference standard will only be used for the qualification and requalification of the working reference standard or new primary reference standard, and the working reference standard is to be used for routine QC purposes and supporting the requalification of primary reference standard if needed.

Regarding stability, the applicant indicates that the primary reference standard has been requalified from preparation date and an appropriate period since the first working reference standard released. The requalification requirements of reference standards are provided. The applicant clarified that the working reference standard is newly prepared and has not yet reached the stability testing period, so there are no requalification results of the working reference standard included. Working reference standards will be requalified at regular intervals.

Container closure system

Storage bags are used as the AS container closure system and specifications are included. The integrity of the outer package and the verification of vendor's Certificate of Analysis is performed. Relevant information on the storage bag, including manufacturer, constructions, materials and size are included. The suitability of storage bag for AS storage has been confirmed by testing according to relevant USP and Ph. Eur. pharmacopeial monographs. Extraction and leachable studies were conducted, no extractables or leachables of toxicology concern at the levels measured, have been identified.

2.3.2.4. Stability

The stability studies were conducted according to ICH Q5C guideline. The stability samples are packed in sterile storage bags. During the procedure, the applicant has updated stability data from the PPQ process AS batches. No out-of-specification results or any significant trends have been observed, thus it is agreed that the current available stability data do not indicate any susceptibility of AS to degradation when stored at long-term storage conditions.

Based on the stability data provided, the proposed shelf-life for the active substance can be agreed.

In addition to the long-term stability studies accelerated stability studies as well as stress stability study and photostability stability studies were performed. The photostability study confirmed that the AS is susceptible to light and thus needs to be protected from light during long-term storage. This is reflected in the SmPC.The applicant commits to complete the ongoing stability studies according to the protocols. After approval, the applicant commits to initiate real-time / long-term stability study for one AS batch annually, unless there is no production in that year. The provided post-approval stability protocol and commitment is acceptable.

2.3.3. Finished Medicinal Product

2 . 3 . 3 . 1 . Description of the product and pharmaceutical development

The finished product Bilprevda has been developed as a biosimilar to reference product Xgeva. The FP is presented as a sterile, clear to slightly opalescent, colourless to slightly yellow solution for injection, containing 70 mg of denosumab as active substance (AS) in 1 mL of solution (70 mg/mL). Other

ingredients are acetic acid glacial, sodium hydroxide (for pH adjustment), sorbitol (E420), polysorbate 20 and water for injections. Composition of FP is provided below.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

Each vial contains 120 mg of denosumab in 1.7 mL of solution (70 mg/mL). An overfill is applied to ensure that the label claim of 1.7 mL can be withdrawn from each vial. There are no overages applied for the FP.

The FP is packaged in a 2 mL single use borosilicate vial (type I glass) with bromobutyl rubber stopper aluminium-plastic combination caps.

A formulation robustness study was performed to show the suitability of the proposed formulation.

The FP manufacturing process is P1.0 and includes: HLX14 AS formulation and mixing, sterile filtration, filling (using a single use aseptic system) and stoppering, capping, visual inspection, labelling and packaging. It has been characterized, resulting in the establishment of PARs for CPPs.

Based on the clinical, pharmacokinetic and the physicochemical characteristics of denosumab, a QTPP was defined.

In line with ICH Q8 (R2), potential CQAs (pCQAs) were derived from the QTPP by linking the expected quality profile to specific attributes of the product. The proposed adjustments for CQAs are acceptable. The FP manufacturing process is well characterized.

Filling volume studies are performed. For single use components, an extractable and leachable risk assessment was performed. Based on these findings, it can be concluded that the risks associated with extractables migrating from the disposable components are negligible.

Regular aseptic simulations (media fills) verify the robustness of the aseptic processing steps. Additional assurance of the microbiological quality of the FP is provided by container closure integrity validation, release testing and stability testing.

2.3.3.2. Manufacture of the product and process controls

All sites involved in manufacture and control of the FP operate in accordance with EU GMP. During the assessment, a Major Objection (MO) was raised, requesting confirmation of GMP compliance to all listed activities of the FP manufacturer. During the procedure confirmation was received and a valid EMA GMP certificate is available. The MO was considered solved.

The FP is manufactured according to a standard process including the following steps: AS Formulation and Mixing, Sterile Filtration, Filling and stoppering, capping, visual inspection, labelling and packaging. The manufacturing process is appropriately described.

Control of critical steps and intermediates

The Control of critical steps and intermediates section describes shortly the process controls in place during the manufacturing of FP manufacturing process and the in-process testing performed to ensure the product quality and integrity are maintained.

The information on how process parameters have been classified into critical and non-critical process parameters is clearly described.

The process performance qualification was performed following a classical approach. For that purpose, PPQ lots of FP were manufactured according to the commercial process in the commercial facility. All PPQ batches met the prospective acceptance criteria and in-process controls, and pre-defined specifications. Hold times are sufficiently justified based on PPQ data. The sterile filtration and filling duration is supported by both aseptic production process time and filter bacteria retention validation study.

In summary, PPQ data demonstrated that the manufacturing process, when it is operated within the established parameters, produce an effective and reproducible medicinal product, which meets the predetermined specifications and quality attributes.

2.3.3.3. Product specification

The specifications for FP for release and shelf-life are provided. Specifications were defined considering ICH Q6B guidance, Ph. Eur. monograph "Monoclonal Antibodies for Human Use" #2031 and include identity, appearance, protein content, potency, purity and impurities and safety. Some of the FP specifications were aligned with the AS specifications, given that the formulation of FP is equivalent to that of AS. Thus, for a discussion of the appropriateness of specifications in common for both AS and FP it is referred to the respective AS section.

The list of quality attributes proposed for FP release and stability testing is acceptable.

Impurities

A risk evaluation concerning the presence of nitrosamine impurities in the FP has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that the risk arising from the possible presence of nitrosamine impurities in the active substance or the related finished product can be considered as negligible. Therefore, no additional control measures are deemed necessary.

The potential presence of elemental impurities in the FP has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment, it can be concluded that the overall risk as regards elemental impurities is negligible and it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

Analytical methods

The methods are performed in compliance with Ph. Eur.: Appearance (colour, clarity), subvisible particles, osmolality, pH, extractable volume, protein content, endotoxin, and sterility, Container Closure Integrity (CCIT). Container closure integrity testing is performed in lieu of sterility testing for FP stability. Sterility is testing in line with Ph. Eur. 2.6.1. Sub-visible particulates are tested using the method described in Ph. Eur. 2.9.19. In-house methods validations were successfully performed

Batch analysis

Batch analysis data for FP manufactured with the commercial process is provided. None of these batches were used for clinical studies. All results of all tested FP batches met the acceptance criteria listed in the specification at the time of the release. The provided batch data confirms manufacturing process consistency.

Reference materials

Reference standard used for finished product testing is the same as for the active substance.

Container closure system

The primary packaging consists of a 2 mL Type I borosilicate glass vial, a 13 mm bromobutyl rubber stopper, and a 13 mm aluminum-plastic combination cap (flip-off aluminium cap). The glass vial complies with Ph. Eur. 3.2.1, the stopper formulation complies with Ph. Eur. 3.2.9. The manufacturers of the primary packaging components are disclosed in the dossier. Procedures applied for sterilization of primary packaging components are briefly described in the dossier. Analytical data performed on the primary packaging components by the finished product manufacturer are provided. Overall information about the primary packaging is sufficient.

2.3.3.4. Stability of the product

The applicant proposes a shelf life for FP vial of 18 months when stored at 5°C ± 3°C, protected from light. based on long-term stability. The stability studies were conducted according to ICH Q5C guideline. The applicant commits to complete the ongoing stability studies according to the protocols. After approval, the applicant commits to initiate real-time / long-term stability study for one FP batch annually, unless there is no production in that year. The provided post-approval stability protocol and commitment is acceptable. Based on the stability data provided, a FP shelf life for 18 months at 5±3℃, protected from light is acceptable.

2.3.3.5. Biosimilarity

In general, a sound and well-established biosimilarity evaluation was performed. HLX14 (denosumab) developed as a biosimilar medicinal product against both EU approved RMPs, Prolia and Xgeva. HLX14 was developed in 3 presentations: as 60 mg vial and PFS as biosimilar to Prolia with the same components and composition, and 120 mg, vial as biosimilar to XGEVA with the same components and composition.

In the analytical similarity assessment, both products Prolia and Xgeva were grouped together to establish analytical similarity acceptance criteria. Furthermore, for quality attributes which are not impacted by FP manufacturing process or container closure system, the analytical results of HLX14 products from all three different presentations were grouped together in the statistical analysis for comparing HLX14 with RMPs for demonstrating the analytical similarity between HLX14 and RMPs.

The applicant performed a comprehensive comparability evaluation of the three HLX14 presentations via a 3-way comparability study conducted per ICH Q5E. The comparability evaluation of the different HLX14 presentations addressed relevant physicochemical and biological quality attributes, including primary structure, molecular weight, secondary and tertiary structure, charge variants, glycosylation, size variants, protein content, and biological and immunological properties.

For most of the quality attributes, the results indicate comparability between the different HLX14 presentations. However, for certain attributes slight differences were observed. It should be noted that these differences were minor (the magnitude of the differences was small) and partly due to rather narrow comparability criteria. Acceptable justifications for all observed differences were provided, and the residual uncertainty due to these differences was considered negligible and did not preclude the

comparability among the three presentations of HLX14. Finally, a comparable degradation under various stress conditions further supports the comparability claim.

In summary comparability of the presentations of HLX14 (60 mg in vial, 60 mg in PFS, and 120 mg in vial) could be demonstrated. Thus, the analytical results of HLX14 products from all three different presentations can be grouped together in the statistical analysis for comparing HLX14 with the reference medicinal products.

After the comparability evaluation of the three HLX14 presentations, a pair-wise similarity assessment of the proposed biosimilar HLX14 with its EU-approved reference medicinal products Prolia and Xgeva was performed. In this analytical similarity assessment, Prolia and Xgeva were grouped together to establish analytical similarity acceptance criteria. The analytical results of three HLX14 presentations were also grouped together in the statistical analysis to demonstrate the analytical similarity between HLX14 and RMPs. The panel of standard and state-of-the-art methods used in the comparability evaluation was also the basis for analytical similarity evaluation. Some additional assays for biological and immunological characterisation which were not part of the comparability evaluation were included in the biosimilarity exercise: binding to FcγRIa, FcγRIIIa-V, FcγRIIIa-F, FcγRIIIb by SPR, binding to C1q by an ELISA, and finally an ADCC and CDC assay to confirm absence any Fc mediated effector functions in both, HLX14 and RMP. Finally, the same stress conditions as described in the comparability study were also applied for the similarity assessment. In addition, a head-to-head accelerated stability study at 25±2°C/60±5% RH has been conducted to support analytical similarity between HLX14 and EU-RMPs. It is agreed that the applied analytical portfolio is appropriate for demonstrating similarity at quality level.

The results from the similarity exercise support the biosimilarity claim. For most quality attributes similarity could be shown. For a few quality attributes differences were observed, but appropriately justified.

Finally, all analytical methods used for the similarity assessment were validated or qualified for the intended use. Also, the justification for the selection of a specific analytical method and its limitations were discussed. Based on the provided method qualification results, it can be agreed that the methods are suitable for their intended use.

In summary, the conclusion that biosimilarity versus the EU reference medicinal product has been sufficiently demonstrated, can be agreed.

Table 1 - Summary of analytical similarity assessment results between HLX14 and EU-RMPs

Test Category	Quality Attribute	Results
Primary structure	Amino acid sequence	Identical
	N- and C-terminal sequence	Identical
	Amino acid composition	Similar
	Molecular weight (MW)	Minor differences, which do not impact the efficacy and safety.
	Disulfide linkage	Identical
	IgG2 disulfide isoforms analysis	Minor differences, which do not impact the efficacy and safety.
	Glycosylation site	Identical

Test Category	Quality Attribute	Results
	Post-translational modifications (PTM)	Minor differences, which do not impact the efficacy and safety.
	Free thiols	Similar
Higher order structure	Secondary and tertiary structures	Similar
Charge heterogeneity	Acidic peaks	Minor differences, which do not impact the efficacy of the products.
	Main peak	Minor differences, which do not impact the efficacy of the products.
	Basic peaks	Minor differences, which do not impact the efficacy of the products.
	Isoelectric point	Identical
	Acidic peaks	Minor differences, which do not impact the efficacy of the products.
	Main peak	Minor differences, which do not impact the efficacy of the products.
	Basic peaks	Minor differences, which do not impact the efficacy of the products.
Glycan	Total High mannose	Slightly higher total HM were observed in HLX14, which did not cause differences in clinical PK results.
	Total Afuc	Slightly lower total Afuc and total Gal were observed in HLX14 batches. The differences on total Afuc and total Gal glycan have no impact on the bioactivity of denosumab which lacks ADCC and CDC functions.
	Total Gal	
	Sialylation	Similar
	Sialic acid	Similar
	Monosaccharide	Similar
Size Variants	Aggregates	Similar
		Similar
		Similar
	Monomer	Similar
		Similar
		Similar
	Monomer	Similar
	HC+LC	Similar
Protein content		Similar
Extinction coefficient		Similar
Immunochemical properties	FcγRIa	Similar
	FcγRIIa-R	Similar
	FcγRIIa-H	Similar
	FcγRIIb/c	Similar
	FcγRIIIa-V	Similar
	FcγRIIIa-F	Similar
	FcγRIIIb	Similar
	FcRn	Similar
	C1q	Similar
Bioactivity	Soluble RANKL binding	Similar

Test Category	Quality Attribute	Results
		Similar
	Binding to membrane-bound RANKL	Similar
	Neutralization activity	Similar
	Inhibition of osteoclast differentiation	Similar
	ADCC	Similar
	CDC	Similar
Forced degradation study		Same degradation pathway and similar degradation trend
Accelerated stability study		Same degradation pathway and similar degradation trend

2.3.3.6. Post approval change management protocol(s)

N/A.

2.3.3.7. Adventitious agents

Multiple complementing measures are implemented to ensure product safety with regard to non-viral and viral adventitious agents. The measures include selection and testing of materials, cell banks and process intermediates, testing of microbial attributes as in-process controls and/or at release, implementation and validation of dedicated virus clearance steps and steps contributing to virus reduction. In addition, microbial quality is ensured by process design (low bioburden process, microbial reduction filtrations, sterile filtration, aseptic processing) and sanitisation procedures.

Animal-derived materials

No materials of animal or human origin are used during manufacture of HLX-014 and the cell banks.

Microbial agents

Master cell bank (MCB), Working cell bank (WCB), and End-of-production cells (EOPCs) were tested according to compendial methods for the absence of bacterial, fungal, mycobacteria, or mycoplasma contamination. Absence of mycoplasma is also ensured by routine testing of the unprocessed bulk. Bioburden and endotoxin tests are performed at multiple stages of the AS and FP manufacturing process. At the release stage, AS and FP are tested for bioburden or sterility, respectively, as well as for endotoxin content.

Adventitious viruses

Absence of viruses in MCB, WCB, and EOPCs was determined by a panel of tests covering a broad range of potentially contaminating viruses.

The testing programme for the cell banks and unprocessed harvest applied to demonstrate the absence of non-viral and viral adventitious agents is in line with guideline ICH Q5A and relevant Ph. Eur. monographs.

Virus clearance studies

The virus clearance capacity of the manufacturing process has been assessed in virus clearance studies using small-scale models of the respective large-scale manufacturing steps. The design of the studies is in line with the guidance documents ICH Q5A and CPMP/BWP/268/95. Initially, multiple deficiencies have been identified regarding the viral clearance studies and on the virus clearance capacity of the manufacturing process. Considering the importance of virus clearance for product safety a Major

objection was raised. The requested information on the small-scale models, the virus test systems and associated controls, the number of virus-spiked runs performed, which process fractions have been tested, the kinetics of virus inactivation, and on column re-use and carry-over has been provided. The MO has been addressed satisfactorily and is considered resolved. The virus clearance capacity was evaluated using a suitable panel of viruses.

In summary, the risk for potential contamination and transmission of bacterial, viral, or TSE agents is acceptably low.

2.3.3.8. GMO

Not applicable.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Bilprevda is being developed as a biosimilar product to the EU-licensed Xgeva, having denosumab as the active substance.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Initially raised major objection on the process control strategy which was considered not sufficient for a reliable control of the AS manufacturing process, and on comparability of clinical with the intended commercial active substance have been solved. The MO on the GMP compliance of the manufacturing site was adequately addressed and a valid GMP certificate is available.

A MO regarding the virus clearance capacity of the manufacturing process has been raised and was adequately resolved during the procedure. The risk for potential contamination and transmission of bacterial, viral, or TSE agents is acceptably low.

In general, a sound and well-established biosimilarity evaluation was performed. The results from the similarity exercise support the biosimilarity claim. For most quality attributes similarity could be shown. The observed differences were appropriately justified and are unlikely to have an impact on the safety or efficacy of the product.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Bilprevda is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Data has been presented to give reassurance on viral/TSE safety.

The results from the similarity exercise support the biosimilarity claim.

No quality aspects impacting on the Benefit-Risk balance have been identified.

In conclusion, the dossier presented by the applicant for the Marketing Authorisation Application for Bilprevda contains adequate and complete information, to support the approval of this application from the quality point of view.

2.3.6. Recommendation(s) for future quality development

None.

2.4. Non-clinical aspects

2.4.1. Introduction

Bilprevda (HLX14) is a proposed biosimilar to EU-Xgeva.

The applicant developed three presentations of HLX14; Bildyos (HLX14) 60 mg/mL in vials and HLX14 60 mg in pre-filled syringes were developed as a proposed biosimilar to Prolia, Bilprevda (HLX14) 120 mg (70 mg/mL) in vials was developed as a proposed biosimilar to Xgeva. The proposed indications for both Bildyos and Bilprevda are the same as those of the reference drugs Prolia and Xgeva, respectively. Extensive analytical similarity studies have been performed against the reference product, Prolia and Xgeva, and clinical studies have been performed against the reference product, Prolia.

HLX14 is a recombinant IgG2 fully human monoclonal antibody against the receptor activator of nuclear factor-κB ligand (RANKL) and is produced in mammalian Chinese hamster ovary (CHO) cells. The active substance is denosumab, the same active ingredient of Xgeva. The proposed indications for HLX14 are the same as those currently authorized for the reference product. Same formulation was used for HLX14 as for the RMP.

EMA and FDA guidelines on biosimilar products have been followed: Guideline on similar biological medicinal products (CHMP/437/04 Rev 1), Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/ 42832/2005 Rev 1), EMA guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010), ICH Topic S6 (R1). Preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH, 2011) and FDA Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (FDA, 2015).

HLX14 nonclinical development plan followed EU and US requirements of a stepwise approach as proposed in the EU Guideline on biosimilars (EMA/CHMP/BMWP/403543/2010 and EMEA/CHMP/BMWP/42832/2005 Rev1) and US FDA guidance (FDA-2011-D-0605 and FDA-2017-D-0154). These guidance state that animal studies are in principle only warranted in case the results of the structural and functional data, including in vitro studies are not considered adequate. In general, analytical similarity is considered paramount for the nonclinical comparability exercise, and in vivo models are not considered as sensitive.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

A comprehensive set of in vitro studies were conducted for analytical and functional characterisation and comparison of HLX14 and EU-/US-Prolia/Xgeva to demonstrate biosimilarity. All in vitro studies data were included in the dossier.

Dedicated in-vivo studies were not conducted, which is acceptable.

2.4.2.2. Secondary pharmacodynamic studies

No secondary PD studies are required for biological medicinal products.

2.4.2.3. Safety pharmacology programme

Dedicated safety pharmacology studies are not required for similar biological medicinal products.

2.4.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies are required for similar biological medicinal products.

2.4.3. Pharmacokinetics

No stand-alone comparative PK studies were performed with HLX14 and the reference product.

This is in line with currently effective guidance and thus accepted.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

Not applicable

2.4.4.2. Repeat dose toxicity

Not applicable

2.4.4.3. Genotoxicity

Dedicated studies to determine the genotoxic potential of HLX14 were not conducted. This is in line with currently effective guidance.

2.4.4.4. Carcinogenicity

No studies have been conducted to assess the potential of HLX14 for carcinogenicity. In ICH S6 (R1) guideline (ICH, 2011) and EMA guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev.1), it is advised that other routine toxicological studies such as mutagenicity and carcinogenicity are not required for similar biological medicinal products, unless indicated by results of repeat-dose studies. Also, in the FDA Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference product (FDA, 2015), no further studies are requested when similarity could be demonstrated through extensive structural and functional characterization and animal toxicity studies.

2.4.4.5. Reproductive and developmental toxicity

No reproductive and development toxicity studies including fertility and early embryonic, embryo-foetal, prenatal and postnatal; and off spring/juvenile studies have been performed with HLX14, which

is in line with EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/ 403543/2010), EMA guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev.1) and FDA Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (FDA, 2015).

2.4.5. Ecotoxicity/environmental risk assessment

Use of medicinal product HLX14 is not expected to pose a risk to the environment as the active substance denosumab is a natural product (protein). In addition, dedicated ERA studies are not required for biosimilar medicinal product.

2.4.6. Discussion on non-clinical aspects

A comprehensive set of in vitro studies were conducted for analytical and functional characterisation and comparison of HLX14 and EU-/US-Prolia/Xgeva to demonstrate biosimilarity. All in vitro studies data were included in the Quality part of the dossier (see discussion above).

Dedicated non-clinical in vivo primary pharmacology studies were not conducted, which is acceptable considering the tiered approach for biosimilarity assessment in accordance with EMA guidelines.

In line with the EMA's "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" [EMA/CHMP/BMWP/42832/2005 Rev 01] and the FDA's "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," toxicity studies to assess non-clinical safety, genotoxicity, reproductive and developmental toxicity, and carcinogenicity were not performed, which is acceptable.

Non-clinical pharmacokinetic (PK) studies were not conducted, as these are generally not required for the non-clinical testing of biosimilars.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, HLX14 (denosumab) is not expected to pose a risk to the environment. The applicant provided an adequate rationale for not submitting a full Environmental Risk Assessment (ERA) report, which is consistent with the ERA guideline.

2.4.7. Conclusion on the non-clinical aspects

Based on the in vitro studies provided, HLX14 and the RMP can be considered biosimilar.

Relevant EMA guidelines and scientific advice given by EMA were followed in the development of biosimilar medicinal products. No dedicated non-clinical studies were submitted, which is considered acceptable for this type of biosimilar medicinal product.

No ecotoxicity/environmental risk assessment was submitted. This is accepted given the product characteristics.

The proposed text for section 4.6 and 5.3 of the SmPC is in line with that of the reference product.

From a non-clinical perspective Bilprevda is approvable as a proposed biosimilar to Xgeva.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study number and status	Study design	Subjects	Sample size	Dosage regimen	Study objectives
HLX14-001 (completed)	**Part I**: An open-label, randomized, parallel-controlled, single-dose, pilot study	Healthy Chinese adult male	24 subjects, including 12 in the HLX14 group and 12 in the EU-Prolia® group.	**HLX14:** 60 mg; **EU-Prolia®:** 60 mg. Single subcutaneous injections.	Primary Objective: To compare the PK parameters of HLX14 and EU-Prolia® after a single subcutaneous injection in healthy adult male subjects to further provide basis for the study design of part II. Secondary Objective: To compare the PD, safety, tolerability, and immunogenicity of HLX14 and EU-Prolia®.
	Part II: A double-blind, randomized, four-arm, parallel-controlled, single-dose study	Healthy Chinese adult male	228 subjects, including 58 in the HLX14 group, 57 in the US-Prolia® group, 56 in the EU-Prolia® group, and 57 in the CN-Prolia® group.	**HLX14:** 60 mg; **US-Prolia®:** 60 mg; **EU-Prolia®:** 60 mg; **CN-Prolia®:** 60 mg. Single subcutaneous injections.	Primary Objective: To compare the PK similarity of HLX14 and Prolia® (US, EU, and CN-sourced denosumab) after a single subcutaneous injection in healthy adult male subjects. Secondary Objective: To compare the PD, safety, tolerability, and immunogenicity of HLX14 and Prolia® (US, EU, and CN-sourced denosumab).
HLX14-002-PMOP301 (completed)	A randomized, double-blind, international multicenter, parallel-controlled study	Postmenopausal women with osteoporosis at high risk of fracture	514 subjects, including 256 in the HLX14 group and 258 in the Prolia® group.	**HLX14:** 60 mg; **Prolia®:** 60 mg. 2 doses, once every 6 months subcutaneous injection.	Primary Objectives • 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 PD endpoint between HLX14 and comparator Prolia® in postmenopausal women with osteoporosis at high risk of fracture. Secondary Objectives: • To assess equivalence of secondary clinical efficacy and PD endpoints between HLX14 and comparator Prolia®. Other Objectives: • To compare ICEs rate, safety, PK and immunogenicity between HLX14 and comparator Prolia®.

ICEs=intercurrent events; PD= pharmacodynamics; PK= pharmacokinetics.

2.5.2. Clinical pharmacology

Analytical methods

Method 20BASM202

Denosumab was captured on 96-well plates coated with human RANKL-Fc protein and quantitated with a rabbit anti-HLX14 detection antibody followed by an anti-rabbit IgG HRP conjugate. The standard curve includes nine concentration levels (200 = anchor point, 400 = LLOQ, 800, 1600, 3200, 6400, 10000, 12800 = ULOQ, and 15000 ng/mL = anchor point). Two sets of three QC sample levels (1200, 3000, 9600 ng/mL) are included in each assay run. For validation of accuracy and precision three sets quality control samples comprising five levels (400, 1200, 3000, 9600, and 12800 ng/mL) were used. Standards and quality control samples were prepared by spiking into 100% normal human serum. Concentrations are determined using a weighted 4-parameter logistic fit. All samples are tested in duplicate. Assay run and sample acceptance is evaluated based on the following:

Acceptance Criteria for Standard curve

- The coefficient of variation (%CV) between the duplicate of the back calculated concentrations should be within 20% CV (25% at the LLOQ and ULOQ).
- The percent bias (%bias) of the back-calculated concentration of the standards should be within ± 20% of the nominal concentration (± 25% at the LLOQ and ULOQ).
- At least 75% with a minimum of 6 standards (excluding anchor points) shall meet the above criteria.

Acceptance Criteria for Quality Control Samples

- Two sets of quality control samples (prepared from HLX14) shall be placed on the sample analysis plate, including HQC, MQC and LQC. Three sets of quality control samples (prepared from HLX14 and Prolia, respectively) including ULOQ, HQC, MQC, LQC and LLOQ should be placed on the validation plate. For the assay to be considered acceptable, four out of the six plated QCs and at least one QC from each level must pass the following acceptance criteria:
- The coefficient of variation (%CV) between the duplicate of the back calculated concentrations should be within 20% (25% at LLOQ and ULOQ).
- The percent bias of the back-calculated concentration of the QCs should be within ± 20% of nominal concentration (± 25% at LLOQ and ULOQ).

Unknown Sample Acceptance Criteria

- The mean concentrations of duplicate wells should be CV% ≤20%, otherwise, the sample needs to be re-analyzed.

Method AP-HLX14PK01

Human Rankl-His protein was used as capture protein; quantitation of bound denosumab was accomplished by an HRP-conjugated goat anti-human Igκ antibody. The standard curve includes seven concentration levels (148.0 = LLOQ, 394.6, 739.9, 1479.8, 3946.0, 7891.9, and 9864.9 ng/mL = ULOQ). Two sets of three QC sample levels (443.9, 2466.2, 7398.7 ng/mL) are included in each assay run. For validation of accuracy and precision three sets of quality control samples comprising five levels (148.0, 443.9, 2466.2, 7398.7, and 9864.9 ng/mL) were used. Standards and quality control samples were prepared by spiking into 100% normal human serum. Concentrations are determined using a weighted 4-parameter logistic fit. All samples are tested in duplicate. Assay run and sample acceptance is evaluated based on the following:

Acceptance Criteria for Standard Curve

- The accuracy (expressed as %Bias) of back-calculated values must be within ± 20.0%, or within ± 25.0% for LLOQ and ULOQ.
- The duplicate precision (expressed as %CV) of the duplicate wells must be ≤ 20.0% or ≤ 25.0% for LLOQ and ULOQ.
- At least 75% and a minimum of 6 non-zero calibration standard points must meet above criteria.

Acceptance Criteria for Quality Control Samples

- Each concentration level of QC samples must have %CV ≤ 20.0% (25% for ULOQ and LLOQ) and %Bias within ±20.0% (25% for ULOQ and LLOQ).
- Meanwhile at least two thirds of the total QC samples and at least 50% at each concentration level have %CV ≤20.0% and %Bias within ±20.0%.

Acceptance Criteria for Dilution Quality Controls

- At least 50% dilution QC samples at each concentration level between the adjacent QC samples must have %CV ≤20.0% and %Bias within ±20.0%.
- If the dilution QC fails, samples diluted should be repeated.

Both ELISA methods were fully validated at the respective testing sites. Validation summaries are presented in the following tables (*Note: bioanalytical equivalence between HLX14 and Prolia has been demonstrated as well but not included in the summary tables*).

PD biomarkers

β-CrossLaps/ β-CTX

The bioanalytical method to determine serum concentrations of β-CrossLaps (CTX, β-isomerized C-terminal telopeptides) in the HLX14-001 part I, HLX14-001 part II and HLX14-002-PMOP301 clinical study was a validated method using Roche Cobas 6000 e601 Immunoassay Analyzer and Roche β-CrossLaps/Serum reagents. β-CrossLaps is captured by incubation with an anti-β-CrossLaps antibody followed by addition of streptavidin-coated microparticles and a monoclonal β-CrossLaps-specific antibody labelled with a ruthenium complex. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

Results are determined via a calibration curve which is instrument specifically generated by 2-point calibration and a master curve provided via the reagent barcode. Acceptability of an assay batch is determined based on results for the two calibrators and the two QC samples (LQC, HQC).

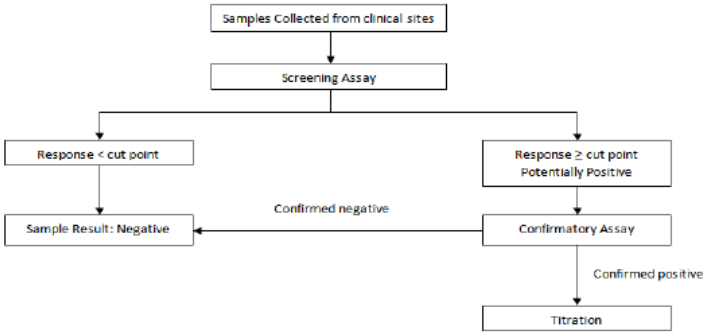
Method validation and sample analysis were performed.

Immunogenicity

3 tiered ADA Assay

The applicant has established an ECL based 3 tiered ADA assay to assess anti-HLX14 and anti-Prolia antibodies. The method is based on HLX14 labeled with biotin and sulfo and uses the classical bridging principle to detect antibodies against HLX14 and anti-Prolia in human serum. Ruthenium in the complex "biotinylated-HLX14-ADA-HLX14-ruthenylated" emits light at 620 nm, which is measured by the MSD Sector Image. Signal intensity is directly proportional to the ADA content in the sample.

Analysis cascade is depicted below:



The assay was validated for Screening Cut Point Factor, Confirmatory Cut Point, Titer Cut Point Factor, Screening sensitivity, Confirmatory sensitivity, Determination of LPC concentration and TPC range, Assay Robustness, Precision, Hook Effect, Selectivity, Drug Tolerance, Target Interference and Stability.

NAb assay

Neutralising potential of induced anti HLX14 and Prolia antibodies was assessed by a functional cell based assay. In brief, a HEK293 cell line was transfected with a plasmid containing RANK receptor and NF-κB gene linked to luciferase. In the presence of HLX14, it will target RANKL to prevent the interaction between RANKL and RANK receptor leading to cell inactivation. If testing samples contain NAbs against HLX14, it will inhibit the activity of HLX14, and RANKL will interact with RANK receptor on HEK293 cell to activate the NF-κB signal pathway and initiate the expression of luciferase through signal transduction. It is expected that all anti-drug antibody (ADA) positive clinical serum samples will contain a high concentration of HLX14 resulting in potential interference in the NAb assay.

The ADA assay and the NAb Assay were revalidated and fulfilled validation criteria.

2.5.2.1. Pharmacokinetics

Study HLX14-001

Study design

HLX14-001 was a randomized, parallel, single-dose, subcutaneous injection, Phase I clinical study of HLX14 versus Prolia (Denosumab) in Chinese Healthy Adult Male Subjects for Comparison in Pharmacokinetic Characteristics, Safety, and Immunogenicity consisting of two parts. The primary objective for part I was to compare the PK parameters of HLX14 and EU-Prolia to further provide basis for the study design of part II, and the primary objective for part II was to compare the PK similarity of HLX14 and Prolia (US, EU, and CN-sourced denosumab). Secondary objectives included comparison of PD, safety, tolerability, and immunogenicity.

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).

Part I of the study was an open-label, randomized, parallel-controlled, single-dose, pilot study conducted in healthy adult male subjects. A total of 24 subjects were planned to be enrolled and randomized at a 1:1 ratio to receive a single subcutaneous injection of 60 mg HLX14 or EU-Prolia (60 mg/mL) with 12 subjects in each group. Subjects received a single dose of HLX14 or EU-Prolia via

subcutaneous injection. Subjects were required to take 600 mg of calcium and 400 IU of vitamin D daily after meals during the study (Day 1 - 134). The dose could be adjusted by the investigators based on the serum calcium level of subjects.

Part II of the study was a double-blinded, randomized, four-arm, parallel-controlled, single-dose study conducted in healthy adult male subjects. 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-sourced Prolia (60 mg/mL).

A total of 228 healthy male subjects were planned to be enrolled and randomized at a 1:1:1:1 ratio to receive a single subcutaneous injection of HLX14 or US, EU, or CN-sourced Prolia, with 57 subjects in each group. Randomization was stratified by weight (≤ 65 kg and > 65 kg). The between-group comparisons included HLX14 versus US-Prolia, HLX14 versus EU-Prolia, HLX14 versus CN-Prolia, US-Prolia versus EU-Prolia, CN-Prolia versus EU-Prolia, and CN-Prolia versus US-Prolia. 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). The dose could be adjusted by investigators based on their serum calcium level.

Pharmacokinetic data analysis

Study HLX14-001

PK parameters were calculated using the non-compartmental analysis (NCA) of WinNonLin software 8.2 or higher, and will be calculated based on the actual PK sample collection time, including AUC0-inf, AUC0-t, Cmax, Tmax, CL/F, λz, t1/2, Vd/F, %AUCex, MRT, AUC0–28d, and AUC0–112d. BLQs are set to zero and included in the PK evaluation before the time of Cmax; BLQs are set to missing in the PK evaluation after the time of Cmax; BLQs are set to missing in the PK evaluation at time points between two measurable concentration values; Consecutive BLQs are set to missing in the PK evaluation at time points between measurable concentrations. Measurable concentrations following consecutive BLQs after the Tmax are set to missing.

PK parameters derived directly from source data (e.g. Cmax) shall be reported with the same precision as the source data, with the exception of Tmax, which will be presented to two decimal places, same with T1/2, MRT and %AUCex. And λz will be presented to four decimal places. All other individual PK parameters will be presented to one decimal place more than the source data with a maximum of 4 decimal places. For the determination of the terminal phase of the concentration-time profile, data was considered insufficient for λz other related parameters (AUC0-inf, AUC0-t, t1/2, CL/F, Vd/F, MRT and etc.) calculation in the following instances, which will be handled as missing for PK parameters summary and analysis of PK similarity:

- Adjusted R2 < 0.8 for calculation of λz by log-linear regression
- Less than 3 data points for λz calculation on the terminal phase
- %AUCex > 20%

Subjects will be included in the PK analysis if their primary PK parameters can be obtained reliably when serum concentration is missing but without affecting the drug absorption, distribution, metabolism and elimination.

Based on PKPS, PK parameters will be summarized by treatment groups. Descriptive statistics as described in the following table (Table 1). For time related parameters (t1/2, Tmax, MRT and etc.), the mean, median, geometric mean, Q1, Q3 and SD will be reported to two decimal places, the same as raw data. Only n, Mean, Min, and Max values will be presented when fewer than three individual PK

parameters are available. And if necessary, sensitivity analysis will be performed to include abnormal data. PK parameters will be listed.

Figure 1: Summary of PK parameters

Table 1 Summary of PK parameters

PK parameters	Statistics
$AUC_{0\text{-}inf}$、$AUC_{0\text{-}t}$、C_{max}、CL/F、λ_z、$t_{1/2}$、V_d/F, $\%AUC_{ex}$, MRT, $AUC_{0–28d}$, $AUC_{0–112d}$	n、Mean、SD、Q1、Median、Q3、Min、Max、CV%、GeoMean、CVb%
T_{max}	n、Q1、Median、Q3、Min、Max

Study HLX14-002-PMOP301

Serum concentration below the limit of quantification (BLQ) were set to zero in statistical summary and will be represented as "BLQ" in data listing. The analysis of PK results will be performed using the Pharmacokinetic Set.

Serum concentrations of HLX14 and Prolia will be summarized at nominal sample time according to treatment group by the following summary statistics. Only n, n of BLQ, arithmetic mean, minimum and maximum values will be presented when fewer than three individual PK concentrations are available.

- The geometric mean (gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- geometric coefficient of variation (CVb%)
- Coefficient of variation (CV, calculated as $100\sqrt{}[\exp(s2)-1]$, where s is the standard deviation of the data on a log scale)
- Gmean ± standard deviation (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observations
- Number of BLQ

A scatter diagram will be plotted using linear and semi-logarithmic coordinates for the arithmetic mean and SD of PK concentrations by treatment group, respectively. Subject PK concentrations will be listed based on the PKS. If necessary, a stratification analysis will be performed for PK concentrations based on the immunogenicity results.

Treatments

Part I of the study

The subjects received a single subcutaneous dose of HLX14 or EU-Prolia on Day 1 by the study nurse at the deltoid muscle area of the upper arm, and the injection site was disinfected as indicated by clinical practice.

Part II of the study

The subjects received a single subcutaneous dose of HLX14 or US, EU, or CN-sourced Prolia on Day 1 by the study nurse at the deltoid muscle area of the upper arm, and the injection site was disinfected as indicated by clinical practice. The actual time of administration was based on the source record. After injection, the subjects were closely monitored by the medical care personnel. In case of hypersensitivity reactions or other symptoms of anaphylaxis with clinical significance, such as hypotension, dyspnea, throat tightness, facial and upper respiratory oedema, itching, urticaria, etc., the investigator should promptly inform the Sponsor and decide whether to provide treatment. Subjects in part II of the study were closely monitored by blinded medical care personnel.

Investigational products:

Investigational Product: HLX14

Product Name	Recombinant anti-RANKL fully human monoclonal antibody (HLX14)
Specifications	60 mg/1 mL/vial
Storage Conditions	2-8 °C away from light
Batch No.	F20200401C, 2203011
Expiry Date	29 April 2023, 26 March 2025
Manufacturer	Shanghai Henlius Biopharmaceuticals Co., Ltd.
Supplier	Shanghai Henlius Biotech, Inc.

Comparator Products: Denosumab (Prolia®)

Product Name	US-sourced Denosumab (US-Prolia®)	EU-sourced Denosumab (EU-Prolia®)	CN-sourced Denosumab (CN-Prolia®)
Specifications	60 mg/1 mL/pre-filled syringe		
Storage Conditions	2-8 °C away from light		
Batch No.	1140672 (US), 1147165 (US)	1142163 (Ireland), 1147037 (Ireland), 1118643 (Ireland)	1137199 (US), 1138365 (US)
Expiry Date	31 October 2024, 31 December 2024	31 August 2024, 31 January 2025, 30 November 2022	29 April 2024
Manufacturer	Amgen Inc.	Amgen Europe B.V.	Amgen Manufacturing Limited
Supplier	Shanghai Henlius Biotech, Inc.		

Non investigational products:

Subjects were required to take 600 mg of calcium and 400 IU of vitamin D daily after meals during the trial (Day 1 - 134). The investigator might adjust the dose of calcium and vitamin D supplements based on serum calcium levels to keep serum calcium concentrations within the normal range.

Treatment compliance:

The investigator should emphasize the importance of compliance to the subject during the conversation about informed consent. During the study, if the subject had poor compliance, the investigator should find out the reasons, actively take corresponding measures (such as emphasizing the importance of protocol compliance to the subject), and completely record the relevant incompliance, reasons, and corresponding measures taken. The clinical research associate should review the treatment compliance during his/her visits to the study site and at the end of the study.

Objectives and endpoints

Primary Pharmacokinetic Endpoints:

- Area under the serum drug concentration-time curve from time 0 to the last concentration-quantifiable time t (AUC_{0-t});
- Maximum serum drug concentration following administration of denosumab (C_{max});
- Area under the serum drug concentration-time curve from time 0 to inf (AUC_{0-inf}).

Secondary Pharmacokinetic Endpoints:

- Time to reach maximum serum drug concentration following administration (T_{max});
- Total clearance (CL/F);
- Apparent terminal elimination rate constant (λz);
- Elimination half-life (t1/2);
- Apparent volume of distribution (Vd/F);
- Area extrapolated from time t to infinity as a percentage of total AUC0–inf (%AUCex);
- Mean residence time (MRT);
- Area under the drug concentration-time curve from Day 0 to Day 28 (4 weeks) and from Day 0 to Day 112 (16 weeks) (AUC0–28d and AUC0–112d).

Pharmacodynamic endpoints:

The PD parameters of s-CTX were calculated with NCA using WinNonLin (v8.2 or later version). Primary PD parameters included:

- Area under the effect-time curve from time 0 to last time of quantifiable concentration of serum C-terminal telopeptide of type I collagen (s-CTX) (AUEC0–t);
- Minimum concentration of s-CTX (I_{min});
- Maximum percent inhibition of s-CTX (I_{max});
- Time to reach I_{min} of s-CTX (T_{min}).

Safety endpoints

- AE and serious adverse event (SAE);

- Physical examinations;
- Vital signs;
- Injection site reactions;
- Laboratory tests (hematology, serum chemistry, and urinalysis);
- 12-lead electrocardiography (ECG).

Immunogenicity endpoints

- Positive rate of anti-drug antibody (ADA);
- Positive rate of neutralizing antibody (NAb).

PK blood sample collection time points

In part I, blood samples for PK analysis were collected: within 2 h before dosing (0 h), and 1 h, 4 h, 8 h (Day 1), 24 h (Day 2), 48 h (Day 3), 96 h (Day 5), 168 h (Day 8), 216 h (Day 10), 264 h (Day 12), 336 h (Day 15), 408 h (Day 18), 504 h (Day 22), 672 h (Day 29), 840 h (Day 36), 1176 h (Day 50), 1512 h (Day 64), 1848 h (Day 78), 2184 h (Day 92), 2520 h (Day 106), 3192 h (Day 134), and 4368 h (Day 183) after the start of dosing (protocol v2.0).

In part II, blood samples for PK analysis were collected: within 2 h before dosing (0 h), and 1 h, 4 h, 8 h (Day 1), 24 h (Day 2), 48 h (Day 3), 96 h (Day 5), 168 h (Day 8), 216 h (Day 10), 264 h (Day 12), 336 h (Day 15), 408 h (Day 18), 504 h (Day 22), 672 h (Day 29), 840 h (Day 36), 1176 h (Day 50), 1512 h (Day 64), 1848 h (Day 78), 2184 h (Day 92), 2520 h (Day 106), 3192 h (Day 134), 3864 h (Day 162), 4536 h (Day 190),5208 h (Day 218), and 6552 h (Day 274) after the start of dosing. (protocol v5.0).

The volume of each blood sample for PK assessment was about 3.5 mL.

PD (s-CTX) blood sample collection time points

In part I: within 2 h before dosing (0 h), and 24 h (Day 2), 48 h (Day 3), 96 h (Day 5), 168 h (Day 8), 216 h (Day 10), 264 h (Day 12), 336 h (Day 15), 408 h (Day 18), 504 h (Day 22), 672 h (Day 29), 840 h (Day 36), 1176 h (Day 50), 1512 h (Day 64), 1848 h (Day 78), 2184 h (Day 92), 2520 h (Day 106), 3192 h (Day 134), and 4368 h (Day 183) after the start of dosing. (protocol v2.0).

In part II: within 2 h before dosing (0 h), and 24 h (Day 2), 48 h (Day 3), 96 h (Day 5), 168 h (Day 8), 216 h (Day 10), 264 h (Day 12), 336 h (Day 15), 408 h (Day 18), 504 h (Day 22), 672 h (Day 29), 840 h (Day 36), 1176 h (Day 50), 1512 h (Day 64), 1848 h (Day 78), 2184 h (Day 92), 2520 h (Day 106), 3192 h (Day 134), 3864 h (Day 162), 4536 h (Day 190), 5208 h (Day 218), 5880 h (Day 246), and 6552 h (Day 274) after the start of dosing (protocol v5.0).

The volume of each blood sample for s-CTX assessment was about 3.5 mL (PD blood samples were collected under fasting conditions).

Immunogenicity blood sample collection time points

In part I: within 2 h before dosing (0 h), and 672 h (Day 29), 1512 h (Day 64), 2520 h (Day 106), and 4368 h (Day 183) after the start of dosing. (Protocol V2.0).

In part II: within 2 h before dosing (0 h), and 336 h (Day 15), 672 h (Day 29), 1512 h (Day 64), 2520 h (Day 106), 4536 h (Day 190), and 6552 h (Day 274) after the start of dosing (protocol v5.0).

At these time points, blood samples were collected for ADA test, and ADA-positive samples were then tested for NAb. The volume of each blood sample for immunogenicity assessment was about 5 mL The time window was the same as that for PK blood sampling.

Sample size

Part I of the study

PK characteristics could be evaluated with 12 subjects per group. A total of 24 subjects were enrolled (supplements to drop-out cases were not required).

Part 2 of the study

The sample size required in part II of the study was estimated based on the results of part I. Part II of study was a parallel study, where primary endpoints (AUC0-t, AUC0-inf, and Cmax) were tested to compare the biosimilarity in PK of HLX14 vs. US, EU, or CN-sourced Prolia with sequential method. Based on the study results of 24 subjects in part I, the maximum coefficient of variation (CV) of the three primary PK parameters, AUC0-t, AUC0-inf, and Cmax, was approximately 28%. Assuming that the actual geometric mean ratio of HLX14 to Prolia for the primary PK parameters was 0.98, the significance level was set at $\alpha = 0.05$ (two one-tailed tests), the power for each primary endpoint of a single between-group comparison was 97% (overall power was above 90%), and the equivalence interval for the primary endpoint was 80 - 125%, 48 evaluable subjects per group were required. Assuming that PK might not be evaluable in approximately 15% of potential subjects, 228 subjects (57 per group) were planned to be enrolled finally.

Randomization

Subjects who completed all screening procedures and were judged eligible for enrolment in the study were randomized prior to the study drug administration.

In part I of the study, eligible subjects were randomized to treatment group and control group at a 1:1 ratio via random envelope.

In part II of the study, the investigators from each study site assigned each screened subject a unique screening number in a sequential order. If a subject was eligible, the investigator logged in the interactive web/voice response system (IWRS) on Day -1 of the screening period, filled in the screening data, and obtained a unique number (randomization number) and corresponding drug number. The eligible subjects were stratified by weight (≤ 65 kg, > 65 kg) and randomized into various treatment groups at a 1:1:1:1 ratio by the IWRS.

If a randomized subject, regardless of whether he had been administrated by the study drug, discontinued the study treatment for any reason, his random number would not be re-assigned to other subjects. Subjects who withdraw from the study did not participate in this study again.

Blinding

Part I of the Study:

Part I was an open-label study, and therefore blinding was not applicable.

Part II of the Study:

Part II was a randomized and double-blind study to ensure that investigators, relevant study personnel, and subjects were blinded to the study allocation. Due to the differences in the appearance

of the study drugs, the study team were divided into unblinded and blinded group. The study drugs were prepared in an independent dispensing room, and an unblinded dispensing nurse was designated at the study site for drug disposition. Denosumab had already been pre-filled into the injector, while HLX14 must be filled into the syringe. The subject received subcutaneous administration while wearing an eye mask in the treatment room (independent from the dispensing room). The whole procedure was performed by a unblinded nurse to ensure that all other relevant personnel (investigators, CRC and Sponsor) remained blinding (except for the unblinded personnel).

Statistical methods

The statistical analysis was performed according to the SAP (version 1.0, 14 November 2023).

Full analysis set (FAS): including all randomised subjects.

Safety analysis set (SS): including all subjects who are randomised and receive the study drugs. Analyses were performed based on subjects' actual treatment groups. SS is used for all safety analyses (including immunogenicity analysis).

PK concentration set (PKCS): Including all the subjects who are randomised and have received the investigational product with at least one assessable post-dose drug concentration, for whom the absorption, distribution, metabolism, and excretion of the investigational product are not seriously affected. PKCS will be used for PK concentration analysis.

PK parameter set (PKPS): Including all the subjects who are with PK parameters that can be reliably calculated and are without major protocol deviations that may significantly affect the calculation of PK parameters. Subjects who are excluded from PKPS include but are not limited to the following conditions: a) The subject is enrolled with serious protocol deviations, due to which the calculation of PK parameters is affected or the parameters cannot be estimated; b) The subject is detected a drug concentration before the first administration greater than 5% Cmax; c) Concomitant medications are administered during the trial that affect the PK parameters. PKPS is used for PK parameter analysis and used as the primary analysis set for the equivalence analysis.

PD parameter analysis data set: Including all the subjects who are randomised and have received the investigational product with primary PD parameters that can be reliably calculated at least.

All analyses were performed on the basis of "receive the study drugs", that is, the data obtained from subjects who are randomised but do not receive the study drugs are excluded from analyses.

For the determination of the terminal phase of the concentration-time profile, data was considered insufficient for λz and other related parameters (AUC0-inf, AUC0-t, t1/2, CL/F, Vd/F, MRT and etc.) calculation in the following instances, which were handled as missing for PK parameters summary and analysis of PK similarity:

• Adjusted R2 < 0.8 for calculation of λz by log-linear regression

• Less than 3 data points for λz calculation on the terminal phase

• %AUCex > 20%

Before database lock, the analysis population is finalised in a data review meeting.

Unless otherwise specified, descriptive statistics for continuous data included number of subjects, arithmetic mean, standard deviation, median, maximum and minimum. Descriptive statistics of PK concentration and PK parameters also included coefficient of variation (CV%), geometric mean and geometric coefficient of variation. Descriptive statistics of categorical data included number of subjects,

percentage. If the number of subjects was 0, the percentage was not presented. Unless otherwise specified, the denominator for percentage calculation was the total number of subjects in the corresponding arm of the corresponding analysis population.

Unless otherwise specified, statistical analyses were performed using Statistical Analysis Software (SAS) version 9.4 or later version. PK and PD parameter analyses were performed using Phoenix WinNonlin software version 8.2 or later version (Certara, L.P., USA).

PK bioequivalence analysis will be provided only for the part II of the study. The primary PK parameters AUC0-t, Cmax and AUC0-inf will be log-transformed and then analysed by ANOVA. The factor in the ANOVA is the treatment groups. Least squares mean (LSM) for each treatment group, difference of LSM between two-groups and their 90% CIs were calculated. These point estimates and confidence intervals will then be exponentially back-transformed to obtain GMR and associated 90% confidence intervals. If the 90% CI of the geometric mean ratio of AUC0-t, Cmax and AUC0-inf falls completely within the range of 80.00% to 125.00%, it can be proved that the two groups (HLX14 and US Prolia, HLX14 and EU-Prolia, HLX14 and CN-Prolia, US-Prolia and EU-Prolia, CN-Prolia and EU-Prolia, CN-Prolia and US-Prolia) have PK bioequivalence.

Conduct of study

Recruitment

Study initiation date: 03 November 2020 (first subject enrolled)

Study completion date: 12 September 2023 (last subject completed)

Database lock: 17 November 2023

Part I of the study was conducted in 1 site in China, while part II was conducted in a total of 3 study sites, all situated in China.

Amendments

The version 1.0 of the Statistical Analysis Plan (SAP) was finalized and became effective on 14 November 2023.

The version 1.0 of the protocol was finalized and became effective on 29 June 2020. The protocol was amended 4 times, resulting in version 2.0 (6 August 2020), version 3.0 (7 May 2022), version 4.0 (15 July 2022) and version 5.0 (18 November 2022).

Major Changes from Version 1.0 (29 June 2020) to 2.0 (6 August 2020):

- Changed the volume of each blood sample for PD evaluation;
- Modified the description of AE relationship;
- Modified the description of expected adverse reaction;
- Added the definition and reporting of SUSAR;
- Updated the description of SAE.

Major Changes from Version 2.0 (6 August 2020) to 3.0 (7 May 2022):

- Modified the number of subjects in part II based on the part I results;
- Added signature page;

- Added the exclusion criteria of "occurrence of fracture or bone-related surgery within 6 months prior to screening" and "vaccination within 1 month prior to screening";
- Modified the inclusion criteria of "Use of any biological products (excluding vaccine) or monoclonal antibodies within 6 months prior to screening" and the method of measuring body temperature during screening period;
- Modified the description of sample size estimation and statistical analysis in part II;
- Added the results of part I;
- Updated the version of WinNonlin;
- Modified the definition of AE according to the GCP-2020;
- Modified the reporting of AESI, AE, SAE as well as SUSAR, and modified the collection time of AE according to the lasted policies;
- Modified the statistical description of PK parameters and PD parameters (s-CTX1).

Major Changes from Version 3.0 (7 May 2022) to 4.0 (15 July 2022):

- Prolonged the follow-up period to 274 days in accordance with EMA's advice, and added corresponding PD, PK and immunogenicity blood sample collection time points;
- Modified the age range in the inclusion criteria in accordance with FDA's advice to prevent subjects with unmatured bone development from being enrolled;
- Modified the prior treatment limitation in exclusion criteria;
- Added AUC0-28d, AUC0-112d, %AUCex and MRT as two PK secondary endpoints in accordance with EMA's advice;
- Added weight as the stratification factor in accordance with EMA's advice;
- Added the exclusion criteria of PKPS in accordance with EMA's advice;
- Subdivided pharmacokinetic set (PKS) as PKCS and PKPS;
- Clarified that the PK parameters were analyzed by treatment groups in descriptive statistics;
- Added 95% CI to evaluate PD parameters in accordance with EMA's advice.

Major Changes from Version 4.0 (15 July 2022) to 5.0 (18 November 2022):

- Added PK blood sample collection time points in accordance with EMA's advice;
- Revised sample size description and statistical description in accordance with EMA's advice;
- Revised the description of equivalence evaluation;
- Updated the description of the re-screening;
- Added prohibited medications: alpha-calciferol and vitamin D analogues;
- Added urea to serum chemistry evaluation;
- Deleted the description of "completed within 30 min before blood collection" in vital signs measurement of the study procedures;
- Revised the limitation time of contraception, sperm donation and smoking until the end of the study.

Participant flow and numbers analysed

Part I of the study

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. No subjects experienced major protocol deviations in part I of the study.

Table 1. ***Subject Disposition in Part I of the Study (All Screened Subjects)***

	HLX14 (N=12)	EU-Prolia® (N=12)	Total (N=24)
Subjects Screened			155
Screen Failure			117 (75.5)
Randomization, n (%)	12 (100)	12 (100)	24 (100) [1]
Subjects Treated, n (%)	12 (100)	12 (100)	24 (100)
Subjects not Treated, n (%)	0	0	0
Completed Study, n (%)	12 (100)	12 (100)	24 (100)
Discontinued from Study, n (%)	0	0	0
Reason for Discontinuation, n (%)			
Consent Withdrawal	0	0	0
Adverse Event	0	0	0
Death	0	0	0
Physician Decision	0	0	0
Poor Compliance and Fails to Attend Follow-up in Time	0	0	0
Serious Protocol Violation	0	0	0
Study Terminated by Regulatory Authorities	0	0	0
Study Terminated by Sponsor	0	0	0
Other	0	0	0

Percentage of screen failure is calculated using the number of screened subjects as denominator and other percentages are calculated using the number of randomized subjects as denominator.
[1] 14 Screen success subjects were not randomized due to "24 subjects were already enrolled into sche duled cohort".
Data source: Table 14.1.1.1-Part1

Table 8 Study Population in Part I of the Study (Full Analysis Set)

	HLX14 (N=12)	EU-Prolia® (N=12)	Total (N=24)
Full Analysis Set (FAS), n (%)	12 (100)	12 (100)	24 (100)
PK Concentration Set (PKCS), n (%)	12 (100)	12 (100)	24 (100)
PK Parameter Set (PKPS), n (%)	12 (100)	12 (100)	24 (100)
PD Concentration Set (PDCS), n (%)	12 (100)	12 (100)	24 (100)
PD Parameter Set (PDPS), n (%)	12 (100)	12 (100)	24 (100)
Safety Set (SS), n (%)	12 (100)	12 (100)	24 (100)

Data source: Table 14.1.3.1-Part1

Part II of the study

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%).

A total of 68 (29.8%) subjects had at least one major protocol deviation, including 21 (36.2%) subjects in the HLX14 group, 16 (28.1%) subjects in the US-Prolia group, 19 (33.9%) subjects in the EU-Prolia group, and 12 (21.1%) subjects in the CN-Prolia group. The major protocol deviations were deviations from visit schedule (67 subjects, 29.4%) and disallowed medication (2 subjects, 0.9%).

A total of 48 (21.1%) subjects had at least one COVID-19-related major protocol deviation, including 13 (22.4%) subjects in the HLX14 group, 13 (22.8%) subjects in the US-Prolia group, 12 (21.4%) subjects in the EU-Prolia group, and 10 (17.5%) subjects in the CN-Prolia group. The COVID-19-related major protocol deviation was deviation from visit schedule (48 subjects, 21.1%).

Table 2. ***Subject Disposition in Part II of the Study (All Screened Subjects)***

	HLX14	US-Prolia®	EU-Prolia®	CN-Prolia®	Total
Subjects Screened					1030
Screen Failure					802 (77.9)
Randomization, n (%)	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
Subjects Treated, n (%)	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
Subjects not Treated, n (%)	0	0	0	0	0
Completed Study, n (%)	54 (93.1)	53 (93.0)	53 (94.6)	53(93.0)	213 (93.4)
Discontinued from Study, n (%)	4 (6.9)	4 (7.0)	3 (5.4)	4(7.0)	15 (6.6)
Reason for Discontinuation, n (%)					
Consent Withdrawal	0	0	0	0	0
Adverse Event	0	0	0	0	0
Death	0	0	0	0	0
Physician Decision	0	0	0	0	0
Poor Compliance and Fails to Attend Follow-up in Time	1 (1.7)	2 (3.5)	1 (1.8)	2 (3.5)	6 (2.6)
Serious Protocol Violation	0	0	0	0	0
Study Terminated by Regulatory Authorities	0	0	0	0	0
Study Terminated by Sponsor	0	0	0	0	0
Lost to Follow-up	1 (1.7)	0	1 (1.8)	0	2 (0.9)
Subject Refuse to Continue the Study	2 (3.4)	2 (3.5)	1 (1.8)	2 (3.5)	7 (3.1)

Percentage of screen failure is calculated using the number of screened subjects as denominator and other percentages are calculated using the number of randomized subjects as denominator.
Data source: Table 14.1.1.1

Table 9 Study Population in Part II of the Study (Full Analysis Set)

	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Total (N=228)
Full Analysis Set (FAS), n (%)	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
PK Concentration Set (PKCS), n (%)	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
PK Parameter Set (PKPS), n (%)	57 (98.3)	56 (98.2)	56 (100)	56 (98.2)	225 (98.7)
The subject is detected a drug concentration before the first administration greater than 5% C_{max}	1 (1.7)	0	0	0	1 (0.4)
Premature drop-out and PK parameters cannot be calculated reliably	0	1(1.8)	0	1 (1.8)	2 (0.9)
PD Concentration Set (PDCS), n (%)	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
PD Parameter Set (PDPS), n (%)	58 (100)	56 (98.2)	56 (100)	56 (98.2)	226 (99.1)
Premature drop-out and PD parameters cannot be calculated reliably	0	1 (1.8)	0	1 (1.8)	2 (0.9)
Safety Set (SS), n (%)	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)

Data source: Table 14.1.3.1

Table 3. **Major Protocol Deviations in Part II of the Study (Full Analysis Set)**

	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Total (N=228)
Subjects with at least one major protocol deviation, n (%)	21 (36.2)	16 (28.1)	19 (33.9)	12 (21.1)	68 (29.8)
Classification of major protocol deviations, n (%)	21 (36.2)	16 (28.1)	19 (33.9)	12 (21.1)	68 (29.8)
Informed Consent	0	0	0	0	0
Disallowed Medications	0	1 (1.8)	0	1 (1.8)	2 (0.9)
IP Admin/Study Treat	0	0	0	0	0
Procedures/Tests	0	0	0	0	0
Include/Exclude Criteria	0	0	0	0	0
Withdrawal Criteria	0	0	0	0	0
AE/SAE	0	0	0	0	0
Visit Schedule	21 (36.2)	16 (28.1)	19 (33.9)	11 (19.3)	67 (29.4)
Other	0	0	0	0	0

Data source: Table 14.1.2.1

Table 4. **Major Protocol Deviations Related to COVID 19 in Part II of the Study**

	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Total (N=228)
Subjects with at least one major protocol deviation, n (%)	13 (22.4)	13 (22.8)	12 (21.4)	10 (17.5)	48 (21.1)
Classification of major protocol deviations, n (%)	13 (22.4)	13 (22.8)	12 (21.4)	10 (17.5)	48 (21.1)
Informed Consent	0	0	0	0	0
Disallowed Medications	0	0	0	0	0
IP Admin/Study Treat	0	0	0	0	0
Procedures/Tests	0	0	0	0	0
Include/Exclude Criteria	0	0	0	0	0
Withdrawal Criteria	0	0	0	0	0
AE/SAE	0	0	0	0	0
Visit Schedule	13 (22.4)	13 (22.8)	12 (21.4)	10 (17.5)	48 (21.1)
Other	0	0	0	0	0

Data source: Table 14.1.2.2

Demographic and other baseline characteristics

Part I of the study

All the subjects (24 [100%]) enrolled in part I of the study were Asian, the median age was 29.5 years (range: 20-49 years). The mean (SD) weight was 64.47 (5.483) kg. The mean (SD) BMI was 22.18 (1.471) kg/m2. All subjects were negative for anti-HIV, HBsAg, anti-HCV, TPPA, alcohol test and tobacco test. No subjects had drug abuse. The results of chest X-ray were all abnormal but with no clinical significance status. The demographic and other baseline characteristics of subjects were well-balanced between the HLX14 group and EU-Prolia group.

Table 5. Demographic and Other Baseline Characteristics in Part I of the Study

	HLX14 (N=12)	EU-Prolia® (N=12)	Total (N=24)
Age (years)			
n	12	12	24
Mean (SD)	31.08 (7.763)	28.92 (7.960)	30.00 (7.768)
Median (Min, Max)	29.00 (22, 45)	30.00 (20, 49)	29.50 (20, 49)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	12 (100)	12 (100)	24 (100)
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	0	0	0
Other	0	0	0
Height (cm)			
n	12	12	24
Mean (SD)	169.53 (3.899)	171.88 (6.845)	170.70 (5.579)
Median (Min, Max)	170.55 (162.1, 174.8)	171.70 (163, 181.5)	171.45 (162.1, 181.5
Weight (kg)			
n	12	12	24
Mean (SD)	64.10 (4.538)	64.83 (6.478)	64.47 (5.483)
Median (Min, Max)	63.65 (56.4, 73.8)	64.80 (54.9, 75.6)	63.83 (54.9, 75.6)
BMI(kg/m^2)[1]			
n	12	12	24
Mean (SD)	22.36 (1.427)	22.00 (1.554)	22.18 (1.471)
Median (Min, Max)	21.90 (20.3, 24.8)	21.80 (19.5, 24.4)	21.90 (19.5, 24.8)

Viral Serology			
Anti-HIV, n (%)			
Positive	0	0	0
Negative	12 (100)	12 (100)	24 (100)
Not Assessable (NA)	0	0	0
Not Done (ND)	0	0	0
HBsAg, n (%)			
Positive	0	0	0
Negative	12 (100)	12 (100)	24 (100)
Not Assessable (NA)	0	0	0
Not Done (ND)	0	0	0
Anti-HCV, n (%)			
Positive	0	0	0
Negative	12 (100)	12 (100)	24 (100)
Not Assessable (NA)	0	0	0
Not Done (ND)	0	0	0
Anti-TP, n (%)			
Positive	0	0	0
Negative	12 (100)	12 (100)	24 (100)
Not Assessable (NA)	0	0	0
Not Done (ND)	0	0	0
Drug Abuse, n (%)			
Positive	0	0	0
Negative	12 (100)	12 (100)	24 (100)
Not Assessable (NA)	0	0	0
Not Done (ND)	0	0	0
Alcohol Test, n (%)			
Positive	0	0	0
Negative	12 (100)	12 (100)	24 (100)
Not Assessable (NA)	0	0	0
Not Done (ND)	0	0	0
Tobacco Test, n (%)			
Positive	0	0	0
Negative	12 (100)	12 (100)	24 (100)
Not Assessable (NA)	0	0	0
Not Done (ND)	0	0	0
Chest Radiological Assessment, n (%)			
Normal	0	0	0
Abnormal-NCS	12 (100)	12 (100)	24 (100)
Abnormal-CS	0	0	0
Not Done (ND)	0	0	0

[1] BMI = Body Mass Index, BMI = Weight (kg) / Height $(m)^2$.
Data source: Table 14.1.4.1-Part1

Part II of the study

All the subjects (228 [100%]) enrolled in part II of the study were Asian, the median age was 34.0 years (range: 28-53 years). The mean (SD) weight was 65.82 (6.652) kg. A total of 111 (48.7%) subjects were ≤ 65 kg and 117 (51.3%) subjects were > 65 kg. The mean (SD) BMI was 23.11 (1.650) kg/m2. All subjects were negative for anti-HIV, HBsAg, anti-HCV, TPPA, alcohol test and tobacco test. No subjects had drug abuse. The results of chest X-ray were all normal or abnormal but with no clinical significance status. The demographic and other baseline characteristics of subjects were well-balanced between the HLX14 group, US-Prolia group, EU-Prolia group, and CN-Prolia group.

Table 6. **Demographic and Other Baseline Characteristics in Part II of the Study (Full Analysis Set)**

	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Total (N=228)
Age (years)					
n	58	57	56	57	228
Mean (SD)	35.00 (5.047)	35.23 (5.295)	34.21 (5.242)	34.81 (5.016)	34.82 (5.130)
Median (Min, Max)	34.00 (28, 48)	34.00 (28, 53)	33.00 (28, 50)	34.00 (28, 47)	34.00 (28, 53)
Race, n (%)					
American Indian or Alaska Native	0	0	0	0	0
Asian	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
Black or African American	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	0	0	0	0	0
Other	0	0	0	0	0
Height (cm)					
n	58	57	56	57	228
Mean (SD)	169.04 (6.067)	168.12 (6.955)	169.61 (6.497)	167.92 (6.136)	168.67 (6.416)
Median (Min, Max)	169.05 (156.7, 184.2)	168.30 (150.6, 182.7)	168.60 (154.7, 188)	168.20 (151.5, 178.3)	168.50 (150.6, 188)
Weight (kg)					
n	58	57	56	57	228
Mean (SD)	65.43 (6.421)	64.97 (6.666)	66.83 (6.241)	66.08 (7.259)	65.82 (6.652)
Median (Min, Max)	65.20 (53, 77.8)	65.10 (50.8, 81.9)	65.23 (56.9, 83.8)	65.40 (50.3, 81.7)	65.20 (50.3, 83.8)
Weight Group, n (%)					
≤ 65 kg	28 (48.3)	28 (49.1)	27 (48.2)	28 (49.1)	111 (48.7)
> 65 kg	30 (51.7)	29 (50.9)	29 (51.8)	29 (50.9)	117 (51.3)
BMI (kg/m^2)[1]					
n	58	57	56	57	228
Mean (SD)	22.86 (1.778)	22.97 (1.595)	23.17 (1.682)	23.45 (1.512)	23.11 (1.650)
Median (Min, Max)	22.60 (19.3, 26)	23.20 (19.3, 25.7)	23.10 (19.3, 26)	23.70 (19.6, 26)	23.20 (19.3, 26)
Viral Serology					
Anti-HIV, n (%)					
Positive	0	0	0	0	0
Negative	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
Not Assessable (NA)	0	0	0	0	0
Not Done (ND)	0	0	0	0	0
HBsAg, n (%)					
Positive	0	0	0	0	0
Negative	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
Not Assessable (NA)	0	0	0	0	0
Not Done (ND)	0	0	0	0	0
Anti-HCV, n (%)					
Positive	0	0	0	0	0
Negative	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)

	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Total (N=228)
Not Assessable (NA)	0	0	0	0	0
Not Done (ND)	0	0	0	0	0
Anti-TP, n (%)					
Positive	0	0	0	0	0
Negative	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
Not Assessable (NA)	0	0	0	0	0
Not Done (ND)	0	0	0	0	0
Drug Abuse, n (%)					
Positive	0	0	0	0	0
Negative	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
Not Done (ND)	0	0	0	0	0
Alcohol Test, n (%)					
Positive	0	0	0	0	0
Negative	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
Not Done (ND)	0	0	0	0	0
Tobacco Test, n (%)					
Positive	0	0	0	0	0
Negative	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
Not Done (ND)	0	0	0	0	0
Chest Radiological Assessment, n (%)					
Normal	29 (50.0)	28 (49.1)	29 (51.8)	27 (47.4)	113 (49.6)
Abnormal-NCS	29 (50.0)	29 (50.9)	27 (48.2)	30 (52.6)	115 (50.4)
Abnormal-CS	0	0	0	0	0
Not Done (ND)	0	0	0	0	0

[1] BMI = Body Mass Index, BMI = Weight (kg) / Height $(m)^2$.
Data source: Table 14.1.4.1

Medical history

In part I, no subjects had medical histories. In part II, a total of 4 (1.8%) subjects had medical histories. The reported medical histories by PT were limb injury (1 subject, 0.4%), upper limb fracture (1 subject, 0.4%), appendicectomy (1 subject, 0.4%), debridement (1 subject, 0.4%), and appendicitis (1 subject, 0.4%).

In both part I and part II, no subjects had prior medications or previously received procedures.

Concomitant medications

In part I of the study, a total of 15 (62.5%) subjects received concomitant medications. The most common concomitant medications (incidence ≥ 10%) by ATC class II were antibacterials for systemic use (16.7%), analgesics (12.5%), antihistamines for systemic use (12.5%), antipruritics, incl. antihistamines, anesthetics, etc. (12.5%) and stomatological preparations (12.5%).

In part II of the study, a total of 89 (39.0%) subjects received concomitant medications. The most common concomitant medications (incidence ≥ 10%) by ATC class II were analgesics (14.0%), anti-inflammatory and antirheumatic products (13.6%), and antibacterials for systemic use (11.8%).

Concomitant procedures

In part I of the study, a total of 3 (12.5%) subjects received concomitant procedures. The reported concomitant procedures by PT were cooling therapy (1 subject, 4.2%), hydrotherapy (1 subject, 4.2%), and tooth restoration (1 subject, 4.2%).

In part II of the study, a total of 2 (0.9%) subjects received concomitant procedure. The reported concomitant procedures by PT were biofeedback therapy (1 subject, 0.4%), electrotherapy (1 subject, 0.4%), kinesitherapy (1 subject, 0.4%), manipulation (1 subject, 0.4%), phytotherapy (1 subject, 0.4%), and tooth restoration (1 subject, 0.4%).

Outcomes

Primary PK endpoints

Pharmacokinetic similarity was not evaluated in part I of the study. In part II of the study, the primary PK parameters AUC0-inf, AUC0-t and Cmax were comparable between the 3 pairs (HLX14 vs US-Prolia, HLX14 vs EU-Prolia, and HLX14 vs CN-Prolia). Of note, for the assessment of biosimilarity to EU-Prolia, the comparison of HLX14 vs EU-Prolia is of primary relevance. The geometric mean ratios (GMRs) for primary PK parameters were comparable across the 3 pairs and were close to 1. The range of 90% CIs for the primary parameters (AUC0-inf, AUC0-t and Cmax) in the 3 pairs contained the value 1. The range of 90% CIs of GMRs for all primary PK endpoints was 0.91 to 1.13 in the 3 pairs, which entirely fell within the pre-specified equivalence margins of 0.80 to 1.25, indicating the PK similarity of HLX14 to US, EU, and CN-sourced Prolia. The results of sensitivity analysis were consistent with the main analysis mentioned above.

Table 7. **Summary of Denosumab Pharmacokinetic Parameters for Bioequivalence by Treatment (PKPS)**

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 11102328, 11103262 and 11103276 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.
Data source: Module 5.3.3.1 HLX14-001 CSR, Table 15.

Sensitivity analyses

The sensitivity analysis 1 was provided to exclude 23 subjects of whom PK concentration in adjacent visits before or after Tmax was missing, considering that their primary PK parameters could not be calculated accurately.

Table 16 Summary of Specific Excluded Subjects in PK Similarity Sensitivity Analysis 1

Treatment Group	Excluded Subjects	Exclusion Reason
HLX14	11101331, 11102190, 11102265, 11103280	PK serum samples in adjacent visits before or after T_{max} was missing, and primary PK parameters could not be calculated accurately
US-Prolia®	11102058, 11102119, 11102273, 11103137, 11103174, 11103238, 11103250	
EU-Prolia®	11101520, 11102103, 11102211, 11103178, 11103184, 11103254	
CN-Prolia®	11102159, 11102209, 11103168, 11103176, 11103262, 11103264	

Table 17 Summary of Denosumab Pharmacokinetic Parameters for Similarity by Treatment-Sensitivity Analysis 1 (PKPS)

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®	53	331.07	49	343.50	0.96	0.89, 1.04	23.23
	HLX14 vs. EU-Prolia®	53	331.07	48	317.35	1.04	0.97, 1.12	22.78
	HLX14 vs. CN-Prolia®	53	331.07	50	336.72	0.98	0.92, 1.05	20.28
	US-Prolia® vs. EU-Prolia®	49	343.50	48	317.35	1.08	0.99, 1.18	25.67
	CN-Prolia® vs. EU-Prolia®	50	336.72	48	317.35	1.06	0.98, 1.14	22.83
	CN-Prolia® vs. US-Prolia®	50	336.72	49	343.50	0.98	0.91, 1.06	23.29
$AUC_{0\text{-}t}$ (day*µg/mL)	HLX14 vs. US-Prolia®	53	320.52	49	331.35	0.97	0.90, 1.04	23.54
	HLX14 vs. EU-Prolia®	53	320.52	48	304.94	1.05	0.97, 1.13	23.32
	HLX14 vs. CN-Prolia®	53	320.52	50	324.15	0.99	0.92, 1.06	20.62
	US-Prolia® vs. EU-Prolia®	49	331.35	48	304.94	1.09	1.00, 1.19	26.23
	CN-Prolia® vs. EU-Prolia®	50	324.15	48	304.94	1.06	0.98, 1.15	23.43
	CN-Prolia® vs. US-Prolia®	50	324.15	49	331.35	0.98	0.90, 1.06	23.66
C_{max} (µg/mL)	HLX14 vs. US-Prolia®	53	5.94	49	5.97	0.99	0.93, 1.07	21.62
	HLX14 vs. EU-Prolia®	53	5.94	50	5.62	1.06	0.99, 1.13	21.33
	HLX14 vs. CN-Prolia®	53	5.94	50	6.12	0.97	0.91, 1.03	19.94
	US-Prolia® vs. EU-Prolia®	49	5.97	50	5.62	1.06	0.98, 1.15	24.92
	CN-Prolia® vs. EU-Prolia®	50	6.12	50	5.62	1.09	1.01, 1.18	23.38
	CN-Prolia® vs. US-Prolia®	50	6.12	49	5.97	1.03	0.95, 1.11	23.67

Note: PK serum samples were missing in adjacent visits before or after T_{max}, C_{max} and AUC could not be calculated accurately, these subjects are not included in equivalence evaluation sensitivity analysis 1.
Due to $\%AUC_{ex}$ of subjects 11102328, 11103262 and 11103276 were greater than 20%, the related PK parameters $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ were not included in equivalence evaluation sensitivity analysis 1.
Data source: Table 14.2.2.4.1

Based on PKPS, the sensitivity analysis 2 included all subjects' primary PK parameters in equivalence evaluation with no exclusion.

Table 18 Summary of Denosumab Pharmacokinetic Parameters for Similarity by Treatment-Sensitivity Analysis 2 (PKPS)

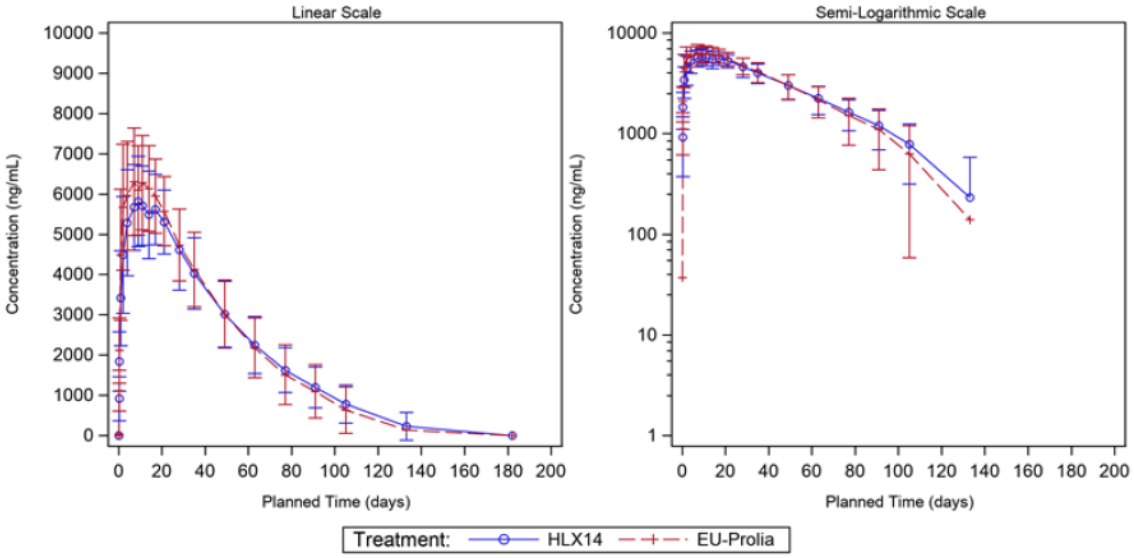
PK parameter (unit)	T vs. R	GeoLSM n	GeoLSM T	GeoLSM n	GeoLSM R	T/R Ratio	90% CI of T/R Ratio	interindividual variability (%)
$AUC_{0\text{-}inf}$ (day*µg/mL)	HLX14 vs. US-Prolia®	57	335.00	56	344.86	0.97	0.91, 1.04	22.88
	HLX14 vs. EU-Prolia®	57	335.00	56	323.56	1.04	0.97, 1.11	22.48
	HLX14 vs. CN-Prolia®	57	335.00	56	340.43	0.98	0.92, 1.05	21.93
	US-Prolia® vs. EU-Prolia®	56	344.86	56	323.56	1.07	0.99, 1.15	24.76
	CN-Prolia® vs. EU-Prolia®	56	340.43	56	323.56	1.05	0.98, 1.13	23.87
	CN-Prolia® vs. US-Prolia®	56	340.43	56	344.86	0.99	0.92, 1.06	24.26
$AUC_{0\text{-}t}$ (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	56	308.35	1.05	0.98, 1.13	22.84
	HLX14 vs. CN-Prolia®	57	324.41	56	325.72	1.00	0.93, 1.06	21.50
	US-Prolia® vs. EU-Prolia®	56	332.62	56	308.35	1.08	1.00, 1.17	25.13
	CN-Prolia® vs. EU-Prolia®	56	325.72	56	308.35	1.06	0.98, 1.14	23.52
	CN-Prolia® vs. US-Prolia®	56	325.72	56	332.62	0.98	0.91, 1.05	23.90
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
	US-Prolia® vs. EU-Prolia®	56	5.99	56	5.65	1.06	0.98, 1.14	24.26
	CN-Prolia® vs. EU-Prolia®	56	6.13	56	5.65	1.09	1.01, 1.17	24.04
	CN-Prolia® vs. US-Prolia®	56	6.13	56	5.99	1.02	0.95, 1.10	23.90

Data source: Table 14.2.2.4.2

Serum drug concentrations

In part I of the study, all 24 subjects treated with investigational and comparator products were included in PK concentration analysis. As shown in the figure below, in part I of the study, after a single dose of HLX14 or EU-Prolia, the profiles of serum denosumab concentration were superimposable, and the PK profiles were similar in both groups.

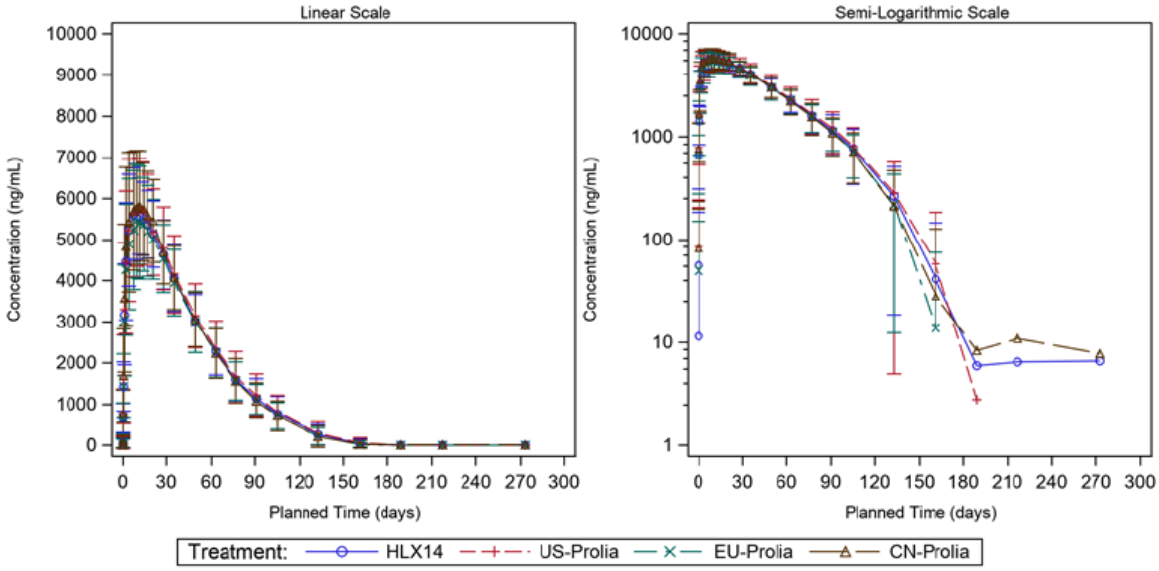
Figure 1. Denosumab Serum Concentration-Time Curves (PKCS)-Part I



Data source: Module 5.3.3.1 HLX14-001 CSR, Figure 1.

As shown in the figure below, **in part II of the study**, after a single dose of HLX14, US-Prolia, EU-Prolia or CN-Prolia, the profiles of serum denosumab concentration were superimposable, with similar PK profiles for all 4 groups. Only 1 subject in the HLX14 group and 1 subject in the CN-Prolia group had detectable plasma denosumab concentrations between Day 190 to Day 274, and only 1 subject in the US-Prolia group had detectable plasma denosumab concentrations on Day 190; while all other subjects were below the lower limit of quantitation by Day 190. Thus, it is suggested that the PK profile in all groups showed a flat trend with concentration near to the lower limit of quantification from Day 190.

Figure 2. Denosumab Serum Concentration-Time Curves (PKCS)-Part II



Data source: Module 5.3.3.1 HLX14-001 CSR, Figure 2.

Summary statistics of pharmacokinetic parameters

In part I of the study, as shown in table below, after HLX14 and EU-Prolia treatment, the serum exposure of denosumab was comparable in two groups. The mean Cmax of HLX14 group and EU-Prolia group were 6.097±0.9819 and 6.735±1.2603 μg/mL. The mean AUC0-t of HLX14 and EU-Prolia were 330.1865±84.4175 and 334.3995 ±89.3640 day*μg/mL; and the mean AUC0-inf were 355.6073±91.7632 and 364.5049±103.4072 day*μg/mL, respectively. The median Tmax of HLX14 and EU-Prolia were 12.48 and 8.99 days; and the mean t1/2 were 28.19±4.22 and 26.81±8.14 days, respectively. Other PK parameters of HLX14 and EU-Prolia were also comparable.

Table 8. **Descriptive Statistics of Denosumab PK Parameters (PKPS)-Part1**

PK Parameter (Unit)	Mean±SD (CV%)			
	n	HLX14 (N=12)	n	EU-Prolia® (N=12)
AUC_{0-inf} (day*μg/mL)	12	355.6073±91.7632 (25.8)	12	364.5049±103.4072 (28.4)
AUC_{0-t} (day*μg/mL)	12	330.1865±84.4175(25.6)	12	334.3995±89.3640 (26.7)
C_{max} (μg/mL)	12	6.097±0.9819 (16.1)	12	6.735±1.2603 (18.7)
*T_{max} (day)	12	12.48 (3.97, 20.98)	12	8.99 (2.00, 16.93)
CL/F (mL/day)	12	179.0709±44.8472(25.0)	12	177.8044±53.4556 (30.1)
λ_z (1/day)	12	0.0251±0.0035 (13.8)	12	0.0278±0.0075 (27.0)
$t_{1/2}$ (day)	12	28.19±4.22 (15.0)	12	26.81±8.14 (30.4)
V_d/F (L)	12	7.0826±1.1602 (16.4)	12	6.4438±1.0452 (16.2)
$\%AUC_{ex}$ (%)	12	7.113±1.0946 (15.4)	12	7.956±2.7497 (34.6)
MRT (day)	12	46.65±7.02 (15.1)	12	43.81±10.45 (23.9)
AUC_{0-28d} (day*μg/mL)	12	145.1127±25.0172(17.2)	12	158.1859±26.8491 (17.0)
AUC_{0-112d} (day*μg/mL)	12	326.4853±73.6947(22.6)	12	336.7953±79.8030 (23.7)

Note: *T_{max} was expressed as Median (Min, Max).
Data source: Table 14.2.2-Part1.

In part II of the study, 225 subjects were included in PK parameters analysis. Three subjects were excluded from PKPS, and detailed information for subjects with special handling for PK parameters analysis was provided. As shown in the table below, after single dose treatment of HLX14, US-Prolia, EU-Prolia and CN-Prolia via subcutaneous injection, the serum exposure of denosumab was comparable in four groups. The mean Cmax of HLX14, US-Prolia, EU-Prolia and CN-Prolia groups were 6.041±1.0418, 6.158±1.4206, 5.804±1.3486 and 6.291±1.4601 μg/mL, respectively. The mean AUC0-t were 331.4480±72.2659, 342.9608±86.6619, 318.1882±76.5436 and 331.1605±71.7708 day*μg/mL; and the mean AUC0-inf were 342.0574±73.6731, 355.2415±87.8928, 330.3393±77.2056 and 343.7000±73.3593 day*μg/mL, respectively.

After a single dose of HLX14, US-Prolia, EU-Prolia and CN-Prolia via subcutaneous injection, the median Tmax were 9.00, 10.99, 10.99 and 9.05 days, respectively; and the mean t1/2 were 21.45±4.54, 22.81±4.30, 22.15±4.62 and 22.67±6.93 days, respectively. Other PK parameters among four groups were also comparable.

Table 9. **Descriptive Statistics of Denosumab PK Parameters (PKPS) (Part2)**

PK Parameter (Unit)	Mean±SD (CV%)							
	n	HLX14 (N=57)	n	US-Prolia® (N=56)	n	EU-Prolia® (N=56)	n	CN-Prolia® (N=56)
$AUC_{0\text{-}inf}$ (day*μg/mL)	57	342.0574±73.6731 (21.5)	56	355.2415±87.8928 (24.7)	54	330.3393±77.2056 (23.4)	55	343.7000±73.3593 (21.3)
$AUC_{0\text{-}t}$ (day*μg/mL)	57	331.4480±72.2659 (21.8)	56	342.9608±86.6619 (25.3)	54	318.1882±76.5436 (24.1)	55	331.1605±71.7708 (21.7)
C_{max} (μg/mL)	57	6.041±1.0418 (17.2)	56	6.158±1.4206 (23.1)	56	5.804±1.3486 (23.2)	56	6.291±1.4601 (23.2)
*T_{max} (day)	57	9.00 (1.98, 21.99)	56	10.99 (2.00, 28.04)	56	10.99 (2.00, 28.03)	56	9.05 (0.99, 21.00)
CL/F (mL/day)	57	182.6191±35.4134 (19.4)	56	179.4327±47.4407 (26.4)	54	192.2278±48.2710 (25.1)	55	182.4771±39.3541 (21.6)
λ_z (1/day)	57	0.0338±0.0075 (22.1)	56	0.0314±0.0058 (18.5)	54	0.0326±0.0067 (20.5)	55	0.0329±0.0088 (26.7)
$t_{1/2}$ (day)	57	21.45±4.54 (21.2)	56	22.81±4.30 (18.8)	54	22.15±4.62 (20.8)	55	22.67±6.93 (30.6)
V_d/F (L)	57	5.5541±1.2804 (23.1)	56	5.7681±1.3085 (22.7)	54	6.0406±1.6295 (27.0)	55	5.8077±1.5419 (26.5)
$\%AUC_{ex}$ (%)	57	3.146±1.6938 (53.8)	56	3.535±1.7429 (49.3)	54	3.814±2.3116 (60.6)	55	3.703±1.9637 (53.0)
MRT (day)	57	43.49±6.26 (14.4)	56	44.58±6.60 (14.8)	54	43.61±5.42 (12.4)	55	43.34±8.56 (19.8)
$AUC_{0\text{-}28d}$ (day*μg/mL)	57	141.6387±24.5109 (17.3)	56	144.9532±32.3713 (22.3)	56	136.8141±30.8727 (22.6)	56	147.9321±31.6943 (21.4)
$AUC_{0\text{-}112d}$ (day*μg/mL)	57	322.8116±62.5021 (19.4)	56	333.1444±76.9538 (23.1)	54	312.3141±69.4498 (22.2)	55	323.8364±61.3391 (18.9)

Note: *T_{max} was expressed as Median (Min, Max).
Due to $\%AUC_{ex}$ of subjects 11102328, 11103262 and 11103276 were greater than 20%, the related PK parameters $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, $\%AUC_{ex}$, V_d/F, CL/F, λ_z, $t_{1/2}$, MRT and $AUC_{0\text{-}112d}$ were not included in summary and equivalence evaluation, but listed.
Data source: Table 14.2.2.1

Table 10. **Summary of Special Handling for PK Parameters Analysis (Part2)**

Treatment Group	Subject	Special Handling	Exclusion reason
HLX14	11102266	Excluded from PKPS	detected with pre-dose concentration greater than 5% C_{max}
US-Prolia®	11101544	Excluded from PKPS	dropped-out prematurely (nearly missed all scheduled blood samples collection after Day 5, except Day 22) before reaching C_{max} and PK parameters could not be calculated reliably
CN-Prolia®	11101156	Excluded from PKPS	dropped-out prematurely (nearly missed all scheduled blood samples collection after Day 5, except EOT) before reaching C_{max} and PK parameters could not be calculated reliably
CN-Prolia®	11103262	The related PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, $\%AUC_{ex}$, V_d/F, CL/F, λ_z, $t_{1/2}$, MRT and $AUC_{0\text{-}112d}$) were excluded from summary	missed scheduled blood samples collection since Day 92 and $\%AUC_{ex}$ of these three subjects were greater than 20%
EU-Prolia®	11102328		
EU-Prolia®	11103276		

Study HLX14-002-PMOP301

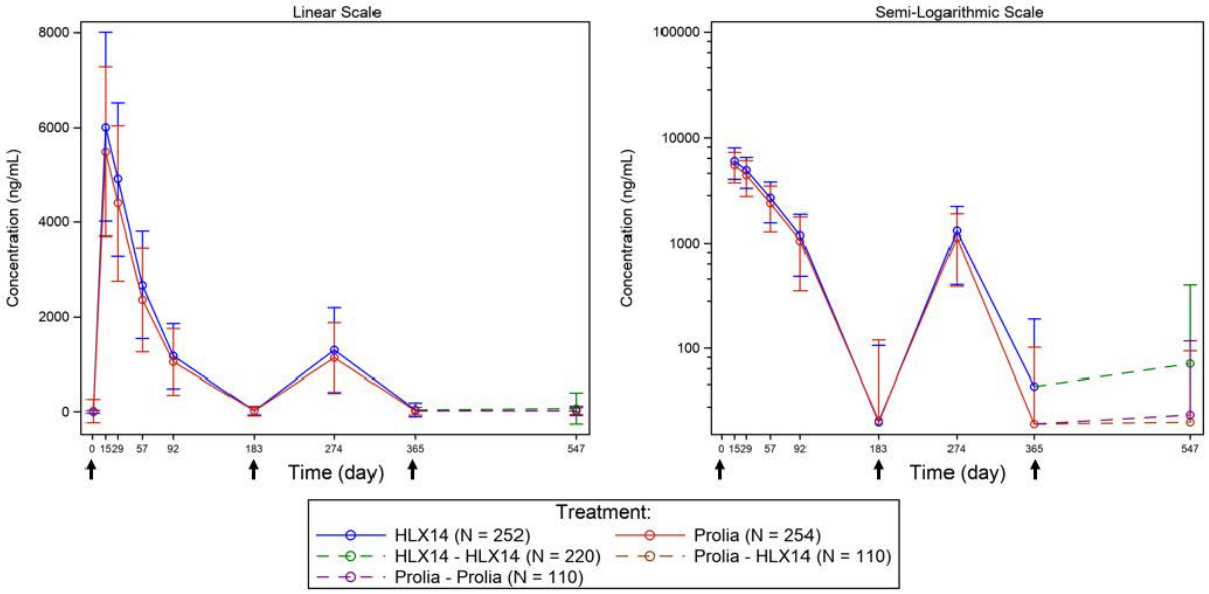
Study HLX14-002-PMOP301 was a randomized, double-blind, international multicentre, parallel-controlled phase III clinical study to evaluate recombinant Anti-RANKL human monoclonal antibody injection (HLX14) versus denosumab injection (Prolia) in postmenopausal women with osteoporosis at high risk of fracture.

Pharmacokinetics results

Based on the PKS, after administration of HLX14 and Prolia, serum denosumab concentration profiles were broadly superimposable, with serum denosumab concentrations at each timepoint being similar between groups across the different treatment periods (HLX14 and Prolia groups in treatment period 1 [from baseline to Week 52]; HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups in treatment period 2 [from Week 52 to Week 78]). A single transition treatment from Prolia to HLX14 did not impact the PK evaluation results (observations at D183 and D365 before transition vs. D547 after transition).

Figure 43: Mean (±SD) Denosumab Serum Concentration Time Data - linear Scale/Semi-logarithmic (X-axis: nominal time) (Pharmacokinetic Set)

Figure 11-8 Mean (±SD) Denosumab Serum Concentration Time Data - linear Scale/Semi-logarithmic (X-axis: nominal time) (Pharmacokinetic Set)



↑ : 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.
Data source: Figure 14.3.8.1.

2.5.2.2. Pharmacodynamics

The pharmacodynamics of HLX14 and the reference products have been investigated in two studies:

- Clinical Phase I study (HLX14-001): A Randomized, Parallel, Single-dose, Subcutaneous Injection, Phase I Clinical Study of HLX14 versus Prolia (Denosumab) in Chinese Healthy Adult Male Subjects for Comparison in Pharmacokinetic Characteristics, Safety, and Immunogenicity
- Clinical Phase III study (HLX14-002-PMOP301): A Randomized, Double-blind, International Multicenter, Parallel-controlled Phase III Clinical Study to Evaluate Recombinant Anti-RANKL Human Monoclonal Antibody Injection (HLX14) versus Denosumab Injection (Prolia) in Postmenopausal Women with Osteoporosis at High Risk of Fracture

Apart from the above-mentioned studies, no other clinical pharmacology studies (i.e., drug interaction studies, or studies in special populations such as hepatic or renal impairment) were performed.

Study HLX14-001

PD Endpoints

- Area under the effect-time curve from time 0 to last time of quantifiable concentration of serum C-terminal telopeptide of type I collagen (s-CTX) (AUEC0-t)
- Minimum concentration of s-CTX (Imin)

- Maximum percent inhibition of s-CTX (Imax)
- Time to reach Imin of s-CTX (Tmin)

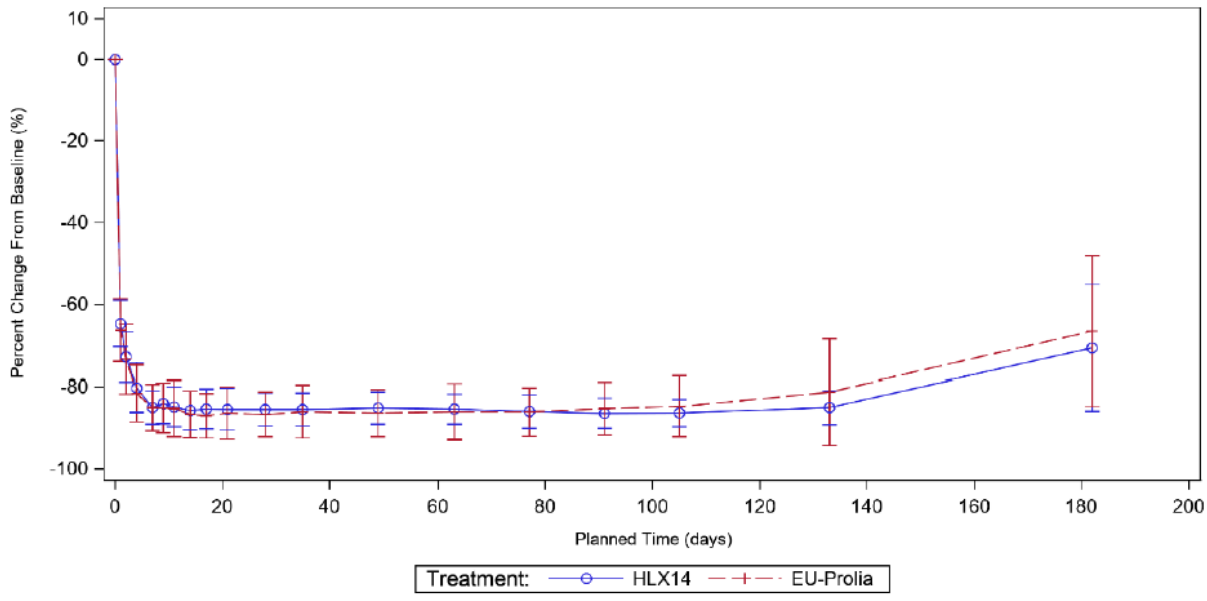
PD Analysis

PD analysis was only conducted in part II of the study. Based on the PDCS, individual subjects' s-CTX concentrations and percent change from baseline values were listed according to the planned sampling time. The s-CTX concentration of PD samples collected 2 hours before administration was defined as the baseline value, and the percentage change of s-CTX relative to the baseline value was calculated as: (s-CTX concentration at a certain time point - baseline s-CTX concentration)/baseline s-CTX concentration * 100. Concentration data below the lower limit of quantification will be expressed as BLQ, which is treated as 1/2 LLOQ when calculating the percent change in s-CTX from baseline. Based on the PDCS, the summary of percentage of changes in s-CTX relative to the baseline value of the subjects will be provided by treatment groups according to the planned sampling time points and descriptive statistics were summarized. The descriptive statistics included n, n of BLQ, Mean, SD, Median, Min, Max, CV%, GeoMean, and CVb%. The percentage change of s-CTX concentration-time curve of each subject will be plotted according to the actual sampling time by treatment groups. The mean percent change in s-CTX concentration (±SD)-time curve was plotted according to the planned sampling time by treatment groups.

For the PD parameters AUEC0-t, Imin, Imax, the between-group GMRs and their 95% CIs will be calculated, but not used for equivalence judgment.

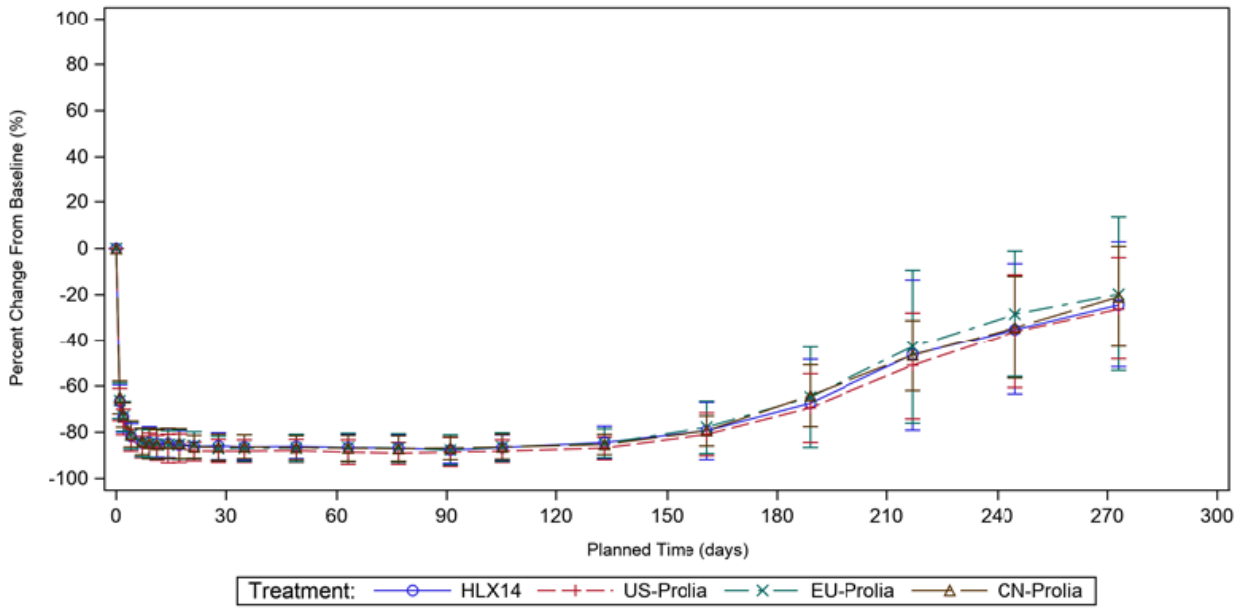
PD results

Figure 4. **Mean (SD) Percent Change from Baseline in s-CTX Concentration-Time Curves (PDCS)-Part1**



Data source: Figure 14.2.4-Part1

Figure 5. **Mean (SD) Percent Change from Baseline in s-CTX Concentration-Time Curves (PDCS)-Part2**



Data source: Figure 14.2.5.1

Figure 6. **Descriptive Statistics of s-CTX PD Parameters (PDPS)-Part1**

PD Parameter (Unit)	Mean±SD (CV%)			
	n	HLX14 (N=12)	n	EU-Prolia® (N=12)
$AUEC_{0-t}$ (day*%inhibition)	12	15114.3714±782.5158 (5.2)	12	14884.2408±1491.8561 (10.0)
***T_{min} (day)**	12	24.47 (6.96, 104.97)	12	16.97 (6.97, 76.95)
I_{min} (ng/mL)	12	0.080±0.0230 (28.7)	12	0.088±0.0439 (49.7)
I_{max} (%inhibition)	12	88.03±3.253 (3.7)	12	88.31±5.003 (5.7)

Note: *T_{min} was expressed as Median (Min, Max).
Data source: Table 14.2.4-Part1.

In part II of the study, 226 subjects were included in PD parameter analysis. One subject in US-Prolia group and one subject in CN-Prolia group dropped-out prematurely (nearly missed most blood samples collection after Day 5) before reaching Imin and PD parameters could not be calculated reliably, thus these two subjects were excluded from PDPS.

Table 11. **Descriptive Statistics of s-CTX PD Parameters (PDPS)**

PD Parameter (Unit)	Mean±SD (CV%)							
	n	HLX14 (N=58)	n	US-Prolia® (N=56)	n	EU-Prolia® (N=56)	n	CN-Prolia® (N=56)
$AUEC_{0-t}$ (day*%inhibition)	58	18984.2642±2923.6544 (15.4)	56	19512.9471±2673.9572 (13.7)	56	18485.5794±3455.6264 (18.7)	56	18639.2033±2764.8797 (14.8)
***T_{min} (day)**	58	28.01 (4.00, 105.01)	56	42.02 (4.00, 105.08)	56	42.03 (7.00, 138.96)	56	28.01 (4.00, 133.99)
I_{min} (ng/mL)	58	0.056±0.0217 (38.6)	56	0.058±0.0238 (41.3)	56	0.058±0.0236 (40.9)	56	0.059±0.0250 (42.3)
I_{max} (%inhibition)	58	89.61±5.064 (5.7)	56	90.95±3.755 (4.1)	56	89.95±4.868 (5.4)	56	89.77±4.330 (4.8)

Note: *T_{min} was expressed as Median (Min, Max).
Data source: Table 14.2.4.1.

In part II of the study, 226 subjects were included in statistical analysis of PD parameters based on PDPS. After a single dose of HLX14, US-Prolia, EU-Prolia and CN-Prolia via subcutaneous injection, descriptive statistical analysis of key s-CTX PD parameters Imax and AUEC0-t has been conducted for all 6 pairs by pairwise comparison (HLX14 vs. US-Prolia, HLX14 vs. EU-Prolia, HLX14 vs. CN-Prolia, US-Prolia vs. EU-Prolia, CN-Prolia vs. EU-Prolia, and CN-Prolia vs. US-Prolia).

The GMRs for key PD parameters (Imax and AUEC0-t) were comparable across the 6 pairs and were close to 1. 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 12. **Summary of Pharmacodynamic Parameters for Similarity by Treatment (PDPS)**

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
	US-Prolia® vs. EU-Prolia®	56	19303.09	56	18013.93	1.07	0.99, 1.16
	CN-Prolia® vs. EU-Prolia®	56	18372.14	56	18013.93	1.02	0.94, 1.11
	CN-Prolia® vs. US-Prolia®	56	18372.14	56	19303.09	0.95	0.89, 1.02
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
	US-Prolia® vs. EU-Prolia®	56	0.05	56	0.05	0.99	0.84, 1.18
	CN-Prolia® vs. EU-Prolia®	56	0.05	56	0.05	1.03	0.87, 1.21
	CN-Prolia® vs. US-Prolia®	56	0.05	56	0.05	1.04	0.88, 1.22
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
	US-Prolia® vs. EU-Prolia®	56	90.88	56	89.82	1.01	0.99, 1.03
	CN-Prolia® vs. EU-Prolia®	56	89.67	56	89.82	1.00	0.98, 1.02
	CN-Prolia® vs. US-Prolia®	56	89.67	56	90.88	0.99	0.97, 1.00

Data source: Table 14.2.4.2

Mechanism of action

RANKL is a transmembrane or soluble essential protein of osteoclasts (responsible for bone resorption) to maintain cell structure, functioning, and survival. Denosumab has a high affinity for RANKL and can prevent RANKL from activating the RANK receptor on the osteoclast surface, thus inhibiting the activation and development of osteoclasts, reducing bone resorption, increasing bone density and strength of cortical and trabecular bones, promoting bone reconstruction, and reducing the incidence of skeletal related events like osteoporosis.

Primary and Secondary pharmacology

Study HLX14-002-PMOP301

Only PD results of study HLX14-002-PMOP301 are discussed in this section.

Results

The geomean (CVb%) of AUEC0-26W for subjects in the HLX14 group vs. Prolia group were 14075.1253 (17.3%) day*%inhibition and 13883.3613 (17.9%) day*%inhibition, respectively. Based on ANOVA model, the geometric LS mean ratio of AUEC0-26W for subjects in the HLX14 group vs. Prolia group was 1.01 (95% CI: 0.98, 1.05), which fell within the pre-specified equivalence margins (0.8, 1.25), confirming the PD equivalence between HLX14 and Prolia.

Primary pharmacodynamic analyses: AUEC0-26W

Table 13. **Summary of Pharmacodynamic Parameters of s-CTX by Treatment (PDS)**

PD Parameter (Unit)	Statistic	HLX14 (N=234)	Prolia® (N=237)
$AUEC_{0\text{-}26W}$ (day * %inhibition)	n	234	237
	Mean	14258.0009	14070.8949
	SD	2036.2958	2009.2307
	CV%	14.3	14.3
	GeoMean	14075.1253	13883.3613
	CVb%	17.3	17.9
	Median	14736.3970	14574.9070
	Min	5983.491	5040.966
	Max	18283.756	16966.267
	Q1	13607.0790	13423.2780
	Q3	15566.9840	15334.6160

$AUEC_{0\text{-}26W}$: area under the effect-time curve for percent changes of s-CTX from baseline to Week 26.
Data source: Module 5.3.5.1 HLX14-002-PMOP301 CSR, Table 11-15.

Table 14. **Analysis of Pharmacodynamic Parameters of s-CTX by Treatment (PDS)**

		GeoLSM						
PD parameter(unit)	T VS R	n	T	n	R	T/R Ratio	90% CI of T/R Ratio	95% CI of T/R Ratio
$AUEC_{0\text{-}26W}$ (day * %inhibition)	HLX14 VS Prolia®	234	14075.13	237	13883.36	1.01	0.99, 1.04	0.98, 1.05

T: Test, R: Reference.
Data source: Module 5.3.5.1 HLX14-002-PMOP301 CSR, Table 11-16.

Supplementary analysis 1: Based on the ITT set, all ICEs applied treatment policy

Table 11-18 Analysis of Pharmacodynamic Parameters of s-CTX by Treatment (Intention-To-Treat set)

PD parameter(unit)	T VS R	GeoLSM n	GeoLSM T	GeoLSM n	GeoLSM R	T/R Ratio	90% CI of T/R Ratio	95% CI of T/R Ratio
$AUEC_{0\text{-}26W}$ (day * %inhibition)	HLX14 VS Prolia®	234	14075.13	237	13883.36	1.01	0.99, 1.04	0.98, 1.05

T: Test, R: Reference.
Data source: Table 14.2.6.3.1.

Supplementary analysis 2: Excluding patients with W0-26 ICEs Major affecting AUEC0-26W

Table 14.2.6.3.3
Analysis of Pharmacodynamic Parameters of s-CTX by Treatment - Supplementary Analysis 2
(Pharmacodynamic Set)

PD parameter(unit)	T VS R	GeoLSM n	GeoLSM T	GeoLSM n	GeoLSM R	T/R Ratio	90% CI of T/R Ratio	95% CI of T/R Ratio
$AUEC_{0\text{-}26W}$ (day * %inhibition)	HLX14 VS Prolia®	231	14171.40	235	13914.13	1.02	0.99, 1.05	0.99, 1.05

T: Test, R: Reference.
Subjects 11103022, 11113025, 11138022, 11139010, 11141002 with w0-26 intercurrent event that major affecting $AUEC_{0\text{-}26W}$ were excluded. Major affecting $AUEC_{0\text{-}26W}$ means patent's $AUEC_{0\text{-}26W}$ deviation from the mean $AUEC_{0\text{-}26W}$ of all subjects are greater than 20%.
Source: Listing 16.2.7.3
[Source: t_adpd_tr.sas] 22MAR2024T2:46:59 EDC DATE: 19JAN2024T10:44:00

Supplementary analysis 3: Excluding patients with W0-26 ICEs or not meeting with inclusion and exclusion criteria and leading to be excluded from PPS

Table 14.2.6.3.4
Analysis of Pharmacodynamic Parameters of s-CTX by Treatment - Supplementary Analysis 3
(Pharmacodynamic Set)

PD parameter(unit)	T VS R	GeoLSM n	GeoLSM T	GeoLSM n	GeoLSM R	T/R Ratio	90% CI of T/R Ratio	95% CI of T/R Ratio
$AUEC_{0\text{-}26W}$ (day * %inhibition)	HLX14 VS Prolia®	228	14045.91	236	13877.75	1.01	0.99, 1.04	0.98, 1.05

T: Test, R: Reference.
Subjects 11104001, 11109020, 11112008, 11124001, 11130031, 11132004, 11136028 were excluded from this table for having w0-26 intercurrent event or not meeting with Inclusion and Exclusion Criteria which leading to be excluded from PPS.
Source: Listing 16.2.7.3
[Source: t_adpd_tr.sas] 22MAR2024T2:47:00 EDC DATE: 19JAN2024T10:44:00

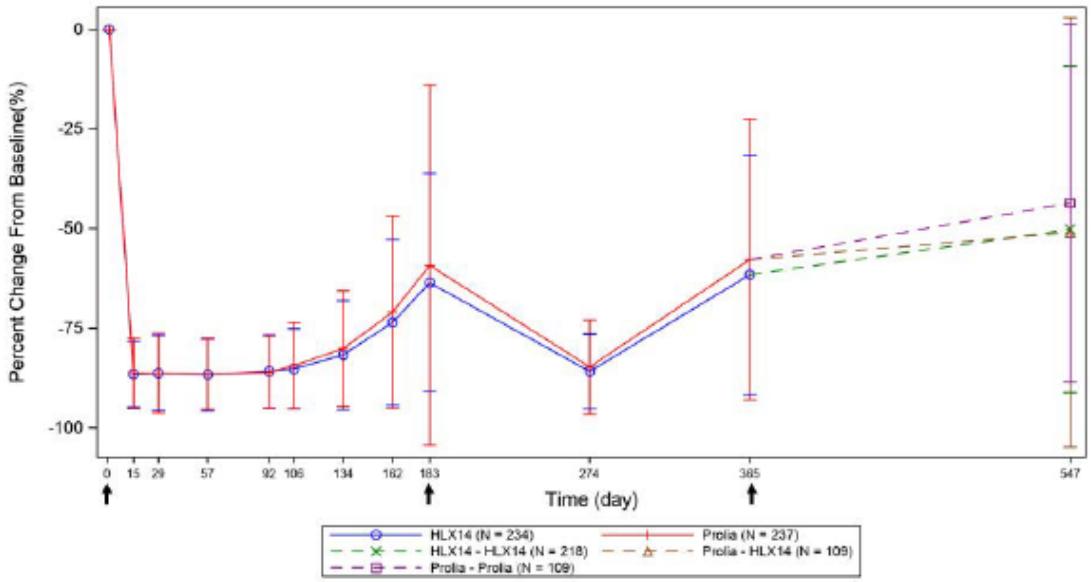
Secondary pharmacodynamic analyses

From baseline to D15, D29, D57, D92, D106, D134, D162, D183, D274, and D365, the LS mean differences (95% CI) for percent changes of s-CTX concentration between the HLX14 group and Prolia group were similar, which showed similar percent changes of s-CTX concentration in both groups.

On D365 and D547, the percent changes in s-CTX and s-P1NP were similar in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups, demonstrating that a single transition treatment from Prolia to HLX14 did not impact the PD evaluation results.

Relative Percent Changes in s-CTX from Baseline to D15, D29, D57, D92, D106, D134, D162, D183, D274, and D365

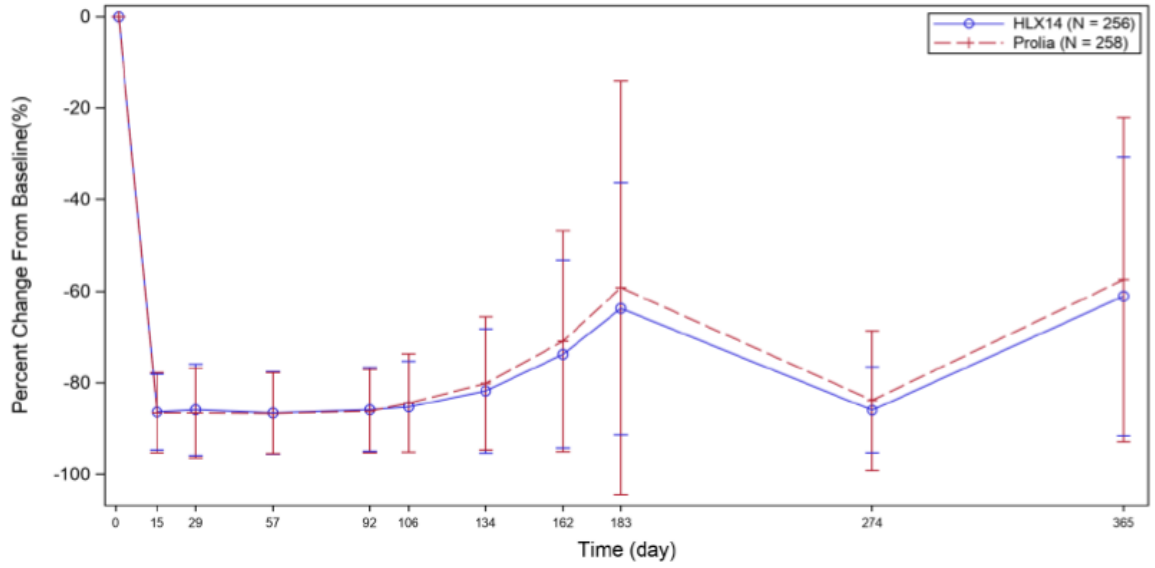
Figure 11-6 Mean(±SD) for Percent Change from Baseline to Week 78 in s-CTX Concentration (Pharmacodynamic Set)



↑ : 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.
Data source: Figure 14.2.13.2.

Supplementary analysis: ITT set

Figure 14.2.6.1.1
Mean(±SD) for Percent Change from Baseline to Week 52 in s-CTX Concentration
(Intention-to-Treat Set)

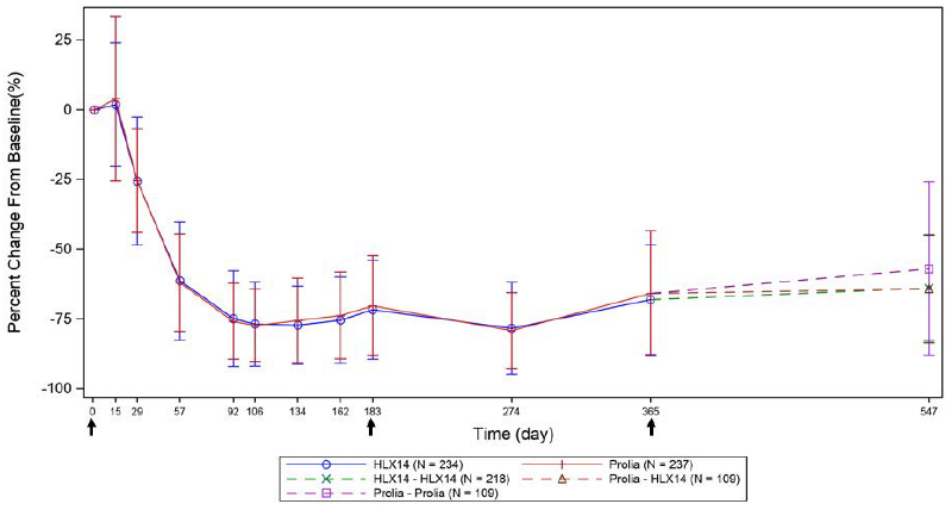


Relative Percent Changes in s-P1NP from Baseline to D15, D29, D57, D92, D106, D134, D162, D183, D274, and D365

From baseline to D15, D29, D57, D92, D106, D134, D162, D183, D274, and D365, the LS mean differences (95% CI) for percent change of s-P1NP concentration between the HLX14 group and Prolia group were similar, which showed similar percent changes of s-P1NP concentration in both groups.

On D365 and D547, the percent changes of s-P1NP concentration in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups were similar, indicating that a single transition treatment from Prolia to HLX14 did not impact the percent change of s-P1NP concentration (observations at D183 and D365 before transition vs. D547 after transition).

Figure 11-7 Mean(±SD) for Percent Change from Baseline to Week 78 in s-P1NP Concentration (Pharmacodynamic Set)



↑ : 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.
Data source: Figure 14.2.14.2.

2.5.3. Discussion on clinical pharmacology

Bioanalytical methods

PK Assays

Two different validated sandwich ELISA methods were used to determine the serum concentration of denosumab in Clinical Phase I study HLX14-001 and the Phase III study HLX14-002-PMOP301. For both methods a single assay approach was chosen for determination of denosumab in serum samples drawn from study subjects treated with HLX14 or Prolia. Method 20BASM202 was used for analysis of samples from Clinical study HLX14-001 Part I; Method AP-HLX14PK01 was used for analysis of samples from Clinical studies HLX14-001 Part II and HLX14-002-PMOP301. The quantification range of the method is 400 – 12,800 ng denosumab/mL (20BASM202) or 148 – 9,865 ng denosumab/mL (AP-HLX14PK01), respectively. Adequate controls are included in each assay run to ensure validity of results.

Both method validations address the requirements of ICH guideline M10 on bioanalytical method validation and study sample analysis (EMA/CHMP/ICH/172948/2019), which came into effect after time of validation. Based on the provided information it is concluded that both methods are adequately validated. Whereas both ELISA methods were used for analysis of PK samples within and across studies, results obtained by the different methods were not combined and thus, cross validation data are not required. Bioanalytical bridging between standards FS201801-RM01 and 2203011-RM02 that

were both used for testing according to Method AP-HLX14PK01 has been demonstrated satisfactorily. Of note, even for the more sensitive Method AP-HLX14PK01 used for the pivotal PK study HLX14-001 Part II the LLOQ is rather high (i.e. 148 ng/mL) and consequently, the serum drug concentration-time curves cannot be fully determined.

Analysis of the study samples is described in detailed analytical reports. Assay performance during clinical sample analysis was comparable to the performance observed during assay validation.

PD assays

β-CrossLaps/ β-CTX

A validated commercially available sandwich immunoassay (Roche Elecsys β-CrossLaps on Roche Cobas 6000 e691 system) was used to determine the concentration of β-CrossLaps in serum samples collected in Clinical studies HLX14-001 Part I and Part II and HLX14-002-PMOP301. The quantification range of the method is 0.039 – 2.32 ng/mL.

Relevant assay performance parameters have been validated. Based on the presented data the method appears sufficiently validated and suitable for the intended purpose.

Analysis of the study samples is described in detailed analytical reports. Performance of the analytical runs in terms of accuracy and precision is consistent with the performance observed during method validation and does not hint at any issue related to testing of the clinical samples.

PINP (N-terminal propeptide of Collagen alpha-1(I) chain)

A validated modified sandwich ELISA kit (Method AP-HLX14BM01) was used to determine the concentration of PINP in serum samples collected in Clinical study HLX14-002-PMOP301. The quantification range of the method is 0.20 – 10.00 ng/mL.

The PINP ELISA method has been validated against criteria that resemble the requirements of ICH guideline M10 on bioanalytical method validation and study sample analysis (EMA/CHMP/ICH/172948/2019). Except for one accuracy/precision run where the intra-assay %bias of the LLOQ QC sample was about -40% (acceptance criterion: ≤25% bias), all validation acceptance criteria were met. To mitigate the higher variability observed at the lower end of the assay range, LLOQ QC samples were included in each clinical assay run. However, despite this, results of the valid clinical assay runs show a somewhat limited precision at the lower end of the assay range. In addition, some potential issues related to haemolytic sera and representativeness of serum samples used to demonstrate selectivity have been identified. Considering that evaluation of PINP is only related to additional secondary endpoints these issues are not further pursued.

Analysis of the study samples is described in a detailed interim analytical report. Performance of the analytical runs in terms of accuracy and precision is consistent with the performance observed during method validation.

Clinical development

The clinical development of HLX14 consisted of two studies to demonstrate PK and PD similarity between HLX14 and Prolia: Phase I Study HLX14-001, consisting of a pilot study and a main study, as well as Phase III Study HLX14-002-PMOP301. No drug interaction studies, or studies in special populations were performed. This is acceptable for biosimilars.

Pharmacokinetics

Phase I Study HLX14-001

Phase I study HLX14-001 was a randomized, double-blind, four-arm, parallel-controlled, single dose study in healthy male volunteers to compare the PK, PD, safety, tolerability and immunogenicity of HLX14, EU-sourced Prolia, US-sourced Prolia, and CN-sourced Prolia. Due to the long half-life of denosumab (mean half-life 28 days), a parallel design rather than a cross-over design is considered appropriate. The study consisted of two parts: an open-label randomized, parallel controlled, two-arm, single dose pilot study comparing the PK, PD safety, immunogenicity, and tolerability of HLX14 and EU-Prolia in 24 volunteers (Part I), and a randomized, double-blind, parallel-controlled, single dose main study to compare the PK, PD, safety, tolerability, and immunogenicity of HLX14 and EU-Prolia, US-Prolia, and CN-Prolia. Part I results were used to calculate Part II sample size. Participants from Part I were not included in Part II and data from both parts were not pooled. General design aspects were discussed in EMA Scientific Advice (EMA/SA/0000084242, EMA/SA/0000099806) and are considered acceptable. In general, CHMP recommendations regarding Phase I design recommendations were adapted, among others prolonging the study period to 9 months to enable characterization of target-mediated elimination and determine similarity of the s-CTX profiles.

The study protocol was amended 4 times and final version 5.0 (18 November 2022) was done following start of the second (pivotal) part of the study (Part II: administration dates: 23/09/2022 - 14/12/2022). This is not considered optimal, nevertheless the changes did not have significant impact on study conduct outcomes and subjects' safety, therefore this is not further pursued.

A single dose of study drug was injected s.c. into the deltoid muscle at day 1, following the posology for Prolia (either thigh, abdomen or upper arm). Subjects were supplemented with Calcium and vitamin D, and serum levels were checked at regular intervals to potentially adjust the supplementation dosage to maintain serum calcium concentrations in the normal range. In part I of the study only HLX-14 and EU-Prolia were compared whereas Part II compared HLX14 and EU-Prolia, US-Prolia, and CN-Prolia. The CoAs of the test product and EU-Prolia have been provided. The protein content in the batches used in both parts of the study HLX14-001 was comparable between the test and the reference product.

The selected dose of 60 mg was discussed during EMA Scientific Advice and considered acceptable, although comparability between treatment groups should be shown for both elimination pathways (EMA/SA/0000084242). The elimination of denosumab is described as biphasic, with a slower initial phase during which serum concentrations decline approximately linearly from the peak, followed by a terminal phase with a more rapid elimination. Differences between HLX14 and the originator in target-mediated and non-specific clearance are difficult to detect using non-compartmental analysis, particularly as the therapeutic flat dose of 60 mg is considered. From the perspective of PD investigation, a 60 mg therapeutic dose for denosumab falls close to the plateau of the dose-response relationship and is less sensitive as compared to lower doses. Although a subtherapeutic dose would have been preferred, the use of a 60mg dose is considered acceptable. It was recommended to include an evaluation of partial AUCs or PK modelling to support the assessment of PK similarity. During SA (EMA/SA/0000099806) the applicant proposed $AUC_{0\text{-}28d}$ and $AUC_{0\text{-}112d}$ to adequately reflect the target-mediated and non-target mediated pathways. According to the literature PK data (Y. Kumagai et al. Bone 49 (2011) 1101–1107; Chen et al. PLoS ONE 13(6), 2018), the linear part of the concentration-time profile starts after 28 days and lasts approximately up to 112 days, while the non-linear clearance primarily drives the elimination at later time points, when serum concentrations fall below 1 ug/ml at week 16. Considering the reported T_{max} values of range from 2 to 28 days for denosumab, the partial $AUC_{0\text{-}28d}$ is expected to contain the absorption phase of the concentration-time profile. The applicant did not justify the cut-off values representative of the linear and non-linear elimination parts of the denosumab concentration-time profile. The results of $AUC_{0\text{-}28d}$ and $AUC_{0\text{-}112d}$ were presented using descriptive statistics. Based on the results that were obtained (discussed below), no additional similarity analysis is necessary to support the comparison.

Based on the posology of Prolia, subjects were supplemented with calcium and vitamin D, which is endorsed. However, PMO patients in the pivotal trials of denosumab generally received a higher dose of at least 1000 mg of oral calcium daily. The applicant did not justify the effects of calcium and vitamin D supplementation and their possible adjustment on study sensitivity to identify PD differences between the treatments. Nevertheless, the pivotal PD data arise from the more relevant patient population in the phase III trial and this is addressed there, therefore this is not further pursued for the healthy volunteer study.

Part I of the study is considered an exploratory pilot study with the objective to inform the confirmatory Part II of the study. The design is operationally seamless and not adaptive as both parts stand on their own. PK objectives investigated in both parts of trial HLX14-001 included 3 primary PK endpoints, (AUC0–t, Cmax, AUC0–inf) as well as several secondary PK endpoints (T_{max}; CL/F; λz; t1/2; Vd/F; %AUCex); MRT; AUC0–28d and AUC0–112d). Additionally, the PD, safety and immunogenicity of HLX14 and Prolia were investigated as secondary endpoints. The selection of endpoints, primary as well as secondary, is considered acceptable and was already discussed during EMA-SA, with the applicant mostly following the advice given by CHMP (adding partial AUCs, %AUCex, MRT) which increases confidence in the results that were finally obtained. Additional PD, safety, and immunogenicity endpoints are also considered acceptable, and the sampling schedule for PK, PD and immunogenicity is considered sufficiently tight to adequately reflect the characteristics of the IMPs.

Considering the reported mean half-life of 25.4 days (SD = 8.5) (EMA/SA/0000084242), more than 9 months is sufficiently long sampling in order to capture the entire elimination profile. However, consideration should be given to whether the sampling time points during the final elimination phase are sensitive to detect potential differences in the target mediated elimination pathway after around 16 weeks. However, after D183, concentration levels would be expected not to be measurable in the majority of subjects. The prolonged study period (from 6 to 9 months) appears not to have augmented PK results, based on the high LLOQ (140 ng/ml) of the assay that was used to measure serum denosumab concentration, which caused the majority of patients not to be able to contribute to the PK results in this extended period from month 6 to month 9. This is discussed further in the PK outcomes section. With this limitation in mind, the objectives and endpoints are considered acceptable with no further questions remaining.

With the maximum coefficient of variation (CV) of approximately 28% of the three primary PK parameters of part I informing sample size planning for part II and also considering a minimal deviation from 1 (true GMR=0.98), 228 subjects were planned to be enrolled and distributed 1:1:1:1 in groups of 57 subjects each for HLX14, EU-Prolia, US-Prolia, and CN-Prolia to achieve a comparison-wise power of at least 97%. No adjustment for multiplicity is needed as all primary endpoints have to fulfil their success criteria. As PK parameters lie within the equivalence margins of 80% to 125%, the sample size was sufficient to achieve the primary success criteria for all endpoints.

The process of randomisation was described in sufficient detail for both part I and part II. Stratification by weight (≤ 65 kg, > 65 kg) in part II was implemented as suggested by CHMP during SA (EMA/SA/0000084242) and is considered beneficial to adjust for the difference in exposure due to the fixed dose and the resulting differences in PK not due to a dissimilarity in treatment.

Blinding in study HLX14-001 was only done in part II as part I of the study was conducted in an open-label manner, although still randomised and controlled. This is acceptable as Part I was only exploratory to inform Part II of the study. Based on the not identical appearance of the IMP, the team was split into an unblinded, and a blinded group. While most of the study personnel remained blinded, and the study participants were blindfolded during administration, the preparing and dosing nurse was unblinded. This potentially introduces bias, as the unblinded dosing nurse was aware of the identity of

the IP during administration. This is considered a limitation, but is often the case for PK studies and not further pursued.

An ANOVA model for the log-transformed primary endpoints with treatment group as a fixed effect is suitable to determine equivalence in terms of the primary endpoints. Equivalence for the primary endpoints (AUC0-t, AUCinf and Cmax) was to be determined if the 90% CI for the ratio of geometric LS means of HLX14 to EU, US, and CN Prolia is within the equivalence range of 0.80 to 1.25, which is in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The applicant also provided ANOVA models where impact of fixed effects of weight (stratification variable used in randomization) and centre on equivalence between HLX14 and EU, US, and CN Prolia, respectively, with respect to primary endpoints was evaluated. Results indicated that 90% CI for the ratio of geometric means was still within equivalence range of 0.80 to 1.25.

After finalization of part I of the study, the applicant sought EMA Scientific Advice regarding the design of part II, and implemented changes based on the recommendations of the CHMP leading to major changes of the study protocol. The changes that were implemented in these versions are supported and are considered beneficial for the ability of the study to generate evaluable results. The exact study initiation date of part II was not specifically mentioned by the applicant. As weight was added as stratification factor in accordance with EMA's advice for version 4 (15 July 2022), this version needed to be finalised before the initiation of part II of the trial. It is unclear if protocol version 5 (18 November 2022) was finalised before study initiation of part II, but the protocol changes had no large impact on the trial conduct.

The participant flow for study HLX14-001 was presented for both part I and part II of the study. In part I of the study, 155 subjects were screened, and 24 subjects were randomized, none of which discontinued the study. In part II, 1030 subjects were screened, 830 of which were considered screening failures. The applicant did not provide details on the nature of the screening failures in both parts of the study.

58, 57, 56, and 57 subjects were randomized to HLX14, US-Prolia, EU-Prolia, and CN-Prolia respectively. The number of subjects that discontinued part II of the study was overall low and the proportion of patients that discontinued were similar between the 4 treatment groups (6.9%, 7.0%, 5.4%, and 7.0% for HLX14, US, EU, and CN-Prolia respectively). No deaths occurred and no subjects discontinued due to adverse events. This raises no further questions.

For the PKPS, only three subjects were excluded from the FAS (1 in the HLX14, US Prolia and CN Prolia group each). For the one subject in the HLX14 group a drug concentration before the first administration greater than 5% Cmax was detected. The other two subjects prematurely dropped out of the study such that PK parameters cannot be calculated reliably.

For the PDPS, only 2 subjects were excluded from the FAS (1 in the US Prolia and CN Prolia group each).

The number of patients with at least one major protocol deviation was comparable between the 4 treatment groups, but higher for HLX14 and EU-Prolia (36.2%, 33.9% for HLX14 and EU-Prolia respectively) compared to US-Prolia and CN-Prolia (28.1% and 21.1%), which is not considered to be concerning. The most common protocol deviation in all four groups was visit schedule related, with other causes for major deviations only occurring in individual cases. The actual observation time-point were used in the analyses. The number of major protocol deviations related to Covid was comparable between the treatment groups, all of which were visit schedule related.

The applicant described the baseline characteristics, medical history, concomitant medications and concomitant procedures for part I and part II. In part I, the baseline characteristics of the two study groups were well balanced, with no notable differences in any metric (age, weight, height, BMI etc.).

No subject had a medical history. 15 patients reported receiving concomitant medications, most of which were antibacterials for systemic use, analgesics, antipruritics, antihistamines, anaesthetics and stomatological preparations. The concomitant medications do not rise concerns based on the comparability in proportion of patients, the type of medication that was administered, the number of subjects involved, and the small size of the study. 3 subjects received concomitant therapies, none of which are considered to be treatment related. In part II, the baseline characteristics between the four study groups were similar in all observed metrics, with no group deviating more than 2 percent from the average in any measure. 4 subjects had medical histories, none of which are considered of any impact to the study. The number of patients taking concomitant medications was generally low, and the proportions of frequently taken medications was comparable. None of the subjects received a concomitant therapy that is considered impactful on the study or concerning.

For the primary analysis of PK similarity, geometric LSmean ratios and their 90% CIs for AUC0-inf, AUC0-t, and Cmax, were calculated for all possible pairings of HLX14, EU-Prolia, US-Prolia and CN-Prolia. Of note, for the conclusion of biosimilarity the comparison of HLX14 vs EU-Prolia is the relevant one. The GMRs for primary PK parameters of HLX14 compared to EU-Prolia were 0.97 (0.91, 1.04), 0.98 (0.91, 1.05) and 0.99 (0.93, 1.06) for AUC0-inf, AUC0-t and Cmax, respectively. Similar results were observed for all other comparisons, with the range of 90% CIs for GMR ranging from 0.90 to 1.17. 3 subjects in the PKPS were excluded from the equivalence evaluations for having $\%AUC_{ex}$ >20%. The number of subjects excluded, in conjunction with the pre-specification of this exclusion strategy in the SAP raises no concerns.

Two sensitivity analyses were performed: 1) excluding subjects of whom PK concentration in adjacent visits before or after Tmax was missing, 2) including all subjects' primary PK parameters in equivalence evaluation with no exclusion. For sensitivity analysis 1 overall 23 subjects were excluded, 4 subjects in the HLX14 group, 7 subjects in the US-Prolia group and 6 subjects each in the EU- and CN-Prolia groups. The GMRs for primary PK parameters (AUC0-inf and AUC0-t and Cmax) were close to 1. The range of 90% CIs for all primary PK endpoints was 0.89 to 1.19 in the 6 pairs and was entirely within the equivalence margins of 0.80 to 1.25. Also, for sensitivity analysis 2, the GMRs for primary PK parameters (AUC0-inf and AUC0-t and Cmax) were close to 1. The range of 90% CIs for all primary PK endpoints was 0.91 to 1.17 in the 6 pairs and was entirely within the equivalence margins of 0.80 to 1.25. Altogether, as the results of the primary PK analyses for the comparison of HLX14 vs EU-Prolia conducted in study HLX14-001 met the equivalence criteria of 0.80 to 1.25, they are considered supportive of biosimilarity of HLX14 and Prolia.

The applicant presented mean concentration-time curves for both part I as well as part II of study HLX14-001. Assay specific concerns are discussed above but primarily concern the relatively high LLOQ of 400 ng/ml for part I and 140 ng/ml for part II. In part I of the study, all 24 subjects were included in the PK analysis of HLX14 against EU-Prolia. Both linear and semi-logarithmic graphs of mean concentration-time curves were presented. The mean concentration-time values were similar up to day 106, after which most subjects had measurements below LLOQ. As the purpose of this study was mainly to inform part II, this is considered acceptable. In part II of the study, all 228 subjects were included in the PK analysis of HLX14 against EU, US, and CN-Prolia. Although the measurements, that were taken resulted in largely overlapping mean concentration-time curves, the following was observed: when the study duration was extended from 6 to 9 months, the assays used to determine denosumab concentrations were not adapted to account for the resulting lower concentration at the end of the observation window. It can be observed that starting with day 162, the majority of subjects was below LLOQ (47/56, 44/55, 50/53 and 49/54 for HLX14, US, EU, and CN-Prolia, respectively). Although this is not ideal, only 3 subjects had %AUC extrapolated >20%, therefore the measurements can still be considered sufficiently reliable. Altogether, the investigation of serum-drug concentration in study HLX14-001 is considered supportive of biosimilarity.

The applicant presented descriptive statistics for all PK parameters for both parts of the study. In part I, the mean AUC0-inf was 355.6073 day*µg/ml and 364.5049 day*µg/ml for HLX14, and EU-Prolia, respectively. The mean AUC0-t was 330.1865 day*µg/ml and 334.3995 day*µg/ml for HLX14 and EU-Prolia, respectively. The mean Cmax was 6.097 µg/ml and 6.735 µg/ml respectively. All other observed PK parameters were comparable as well. In part II of the study, Cmax of HLX14, US-Prolia, EU-Prolia and CN-Prolia were 6.041±1.0418, 6.158±1.4206, 5.804±1.3486 and 6.291.4601 µg/mL, respectively. The mean AUC0-t were 331.4480, 342.9608, 318.1882 and 331.1605 day*µg/mL; and the mean AUC0-inf were 342.0574, 355.2415, 330.3393 and 343.7000 day*µg/mL, respectively. Median Tmax varied between the treatment groups 9.00, 10.99, 10.99, 9.05 for HLX14, US-Prolia, EU-Prolia, and US-Prolia, but this is not considered overly concerning, as this parameter has a large range and variance. CL/F, λz, $t_{1/2}$, V_d/F and MRT were all similar between the treatment groups. As previously discussed, the LLOQ of the assay used to detect serum denosumab concentration is considered relatively high, but the %AUC extrapolated is considered low for all treatment groups at 3.146%, 3.535%, 3.814%, and 3.703% for HLX14, US, EU, CN-Prolia, respectively. AUC0-28d and AUC0-112d were similar for HLX14, US, EU, and CN-Prolia, supporting the similarity in the absorption and non-target mediated denominated clearance phase.

Study HLX14-002-PMOP301

For study HLX14-002-PMO301, serum denosumab concentration-time profiles of HLX14 and Prolia were provided over of the 18-month study period (treatment period 1 & treatment period 2). General study aspects are discussed below in the efficacy section. The serum concentrations of the study drugs at each time point during the trial were investigated as secondary endpoint in this phase III trial.

Overall, the PK profiles for the HLX14 and Prolia were comparable throughout the study period, which is considered supportive of biosimilarity, although mean serum concentrations were higher by around 10% in the HLX14 group from D15 to D92. The PK data from study HLX14-002-PMOP301 are supportive only, as the primary data for PK equivalence were generated in phase I study HLX14-001, which clearly demonstrates PK equivalence between HLX14 vs EU-Prolia. A summary of denosumab serum concentrations from baseline to Week 52 by treatment was presented. The highest mean denosumab concentration was measured on D15 with 6011.1959 ng/mL (SD: 1996.2062) and 5487.52 ng/mL (SD: 1786.1670) for HLX14 and EU-Prolia, which is considered comparable. At D1 pre-dose, measurable denosumab concentrations were detected in six subjects (2, and 4 for HLX14, and Prolia respectively). A similar finding was also observed in study HLX14-001. By request, the applicant provided narratives for the affected subjects. None of the affected subjects stated having received denosumab prior to study initiation, and the finding could not be explained. Nevertheless, while not resolvable this is not considered as questioning clinical biosimilarity between HLX14 and Prolia, and this concern is not further pursued, but is handled as a remaining uncertainty.

Pharmacodynamics

HLX14 was developed as a biosimilar product to Prolia (and Xgeva). The mechanism of action is identical to the reference product(s). The monoclonal antibody denosumab targets and binds to human receptor activator of nuclear factor kappa-B ligand (RANKL), thus preventing interaction of RANKL with receptor activator of nuclear factor kappa-B (RANK). Block of this interaction leads to reduced osteoclast number and function. Thus, bone resorption and cancer-induced bone destruction is decreased. In patients with giant cell tumour of bone, denosumab binds to RANKL, significantly reducing or eliminating osteoclast-like giant cells. The mode of action has been adequately described by the applicant.

The applicant provided an extrapolation report called "Position paper on the extrapolation of HLX14 Data to indications for which licensure is sought", which describes that the mechanism of action is identical across all indications. Thus, based on the same mechanism of action, extrapolation to all

indications might be justified, provided that similarity is shown regarding quality and extended functional characterization and that clinical data show comparability in terms of PK, PD, efficacy and safety.

PD was investigated both in the phase I, as well as the phase III clinical trial, the latter serving as the confirmatory trial to establish PD similarity between HLX14 and Prolia.

Study HLX14-001

In study HLX14-001, only C-telopeptide of type I collagen measured via serum (s-CTX) was measured as PD parameter, with corresponding 4 PD endpoints being presented with descriptive statistics: Area under the effect-time curve from time 0 to last time of quantifiable concentration of serum C-terminal telopeptide of type I collagen (s-CTX) (AUEC0-t); Minimum concentration of s-CTX (Imin); Maximum percent inhibition of s-CTX (Imax); Time to reach Imin of s-CTX (Tmin). PD parameters were only analysed descriptively for part I of the study, which is considered acceptable based on the small number of subjects included in part I of this trial. As proposed in EMA Scientific Advice, the study duration was extended from 6 to 9 months for part II, which is sufficient to characterize s-CTX, and between-group GMRs and their 95% CIs were presented.

Concentration time-graphs, descriptive statistics as well as statistical analysis did not show any clinically relevant difference between the study groups. In part I the s-CTX level seems to return faster towards the baseline level in EU-Prolia group than in the HLX14 group. Since this effect is not observed in the larger part II, this will not be followed further. The GMRs for AUEC0-t and Imax in part II were similar for all treatment pairs and the 95% CIs were entirely contained within the acceptance limits of 80% to 125% (range: 89% to 116%). Imin was also comparable between HLX14 vs. EU-Prolia (T/R Ratio: 0.97, 95% CI: 0.81 – 1.15) and within the equivalence range. Therefore, the PD investigation of study HLX14-001 is considered supportive of biosimilarity with no remaining questions.

Study HLX14-002-PMOP301

In study HLX14-002-POMP3, s-CTX and P1NP were evaluated for PD analysis of HLX14 compared with EU-Prolia. In this section, only PD results are discussed.

In EMA Scientific advice it was recommended to assess the PD primary endpoint s-CTX $AUEC_{0\text{-}26W}$ as co-primary endpoint in addition to the efficacy primary endpoint percent change in BMD from baseline until Week 52, which was followed by the applicant. Percent change from baseline in s-CTX and P1NP were investigated as secondary PD endpoints throughout the study period at regular intervals. Similar to study HLX14-001, PD markers returned to the baseline faster in the EU-Prolia group than in the HLX14 group at the terminal elimination phase. However, in the terminal elimination phase the measurement errors and variability increase, hence, the terminal elimination phase is considered less sensitive for biosimilarity. Therefore, this issue is not pursued further.

Baseline values for s-CTX concentration were similar between HLX14 and EU-Prolia (0.493 ng/ml [SD: 0.2207] for HLX14 and 0.501 ng/ml [SD: 0.2269] for EU-Prolia; ITT set). The primary analysis of $AUEC_{0\text{-}26W}$ for s-CTX comparing HLX14 against EU-Prolia showed a geometric LS mean ratio of 1.01 (95% CI: 0.98, 1.05), which is considered supportive of biosimilarity as it falls within the pre-specified equivalence interval of 80%-125%. The results of the primary analysis are supported by the results of the sensitivity analyses as well as those of the secondary s-CTX endpoint, which showed similarity at all measured time points.

For P1NP, baseline values were similar for HLX14 and EU-Prolia (711.6681 ng/ml (SD: 271.0656) for HLX14, and 683.3119 ng/ml (SD: 290.9356) for Prolia), allowing for a meaningful comparison of the groups in this PD endpoint. The results of the s-P1NP investigation via MMRM for percent change of s-

P1NP concentration from baseline for HLX14 vs. Prolia were similar at all time points with the curves practically overlapping.

Overall, the results of the PD investigation in study HLX14-002-PMOP301 are considered supportive of biosimilarity.

2.5.4. Conclusions on clinical pharmacology

In phase I study HLX14-001, the geometric LSM ratio (90% CI) for HLX14 and EU-Prolia for AUC0-inf, AUC0-t, and Cmax were 0.97 (0.91, 1.04), 0.98 (0.91, 1.05) and 0.99 (0.93, 1.06), respectively. The results were within the equivalence margins of 0.80 to 1.25 and are therefore considered supportive of biosimilarity from a PK perspective. This finding is supported by the comparison of primary AUC parameters between all treatment pairs with a range of 90% CIs of GMRs for all primary PK endpoints being 0.90 to 1.17. Similarity was also demonstrated in all parameters of PD measures s-CTX. The main limitation of study HLX14-001 was the high LOQ of the PK assay, which prohibited the comparison of the IPs during the timepoints where target-mediated clearance dominates.

In phase III study HLX14-002-PMOP301, PK/PD was investigated throughout the currently submitted 12-month main study period. Similar serum concentrations of denosumab were measured at all time points. Similarity was demonstrated in the primary PD endpoint AUEC of s-CTX from baseline to week 26 with a geometric LS mean ratio of 1.01 (95% CI: 0.98, 1.05) for HLX14 compared to Prolia. Secondary PD endpoints were relative changes in s-CTX and P1NP from baseline and support the PD similarity conclusion. Compared to the Phase 1 Study, PK/PD sampling was less frequent, and an unexpected finding of measurable denosumab concentrations in 6 subjects needs to be discussed. Nonetheless, the results of the PK/PD could be supportive of biosimilarity, provided outstanding concerns are resolved.

The mechanism of action of denosumab is identical in all authorized indications, therefore, considering the comparable PK profile of Prolia and Xgeva, the results of the PK/PD investigation using Prolia as a comparator can be extrapolated to demonstrate PK/PD similarity of HLX14 and Xgeva.

2.5.5. Clinical efficacy

Table: Clinical efficacy study

Table 15. Clinical efficacy study

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
HLX14-002-PMOP301	Study status: Completed Study initiation date: Jun 17, 2023	Randomised, double-blind, multicentre	Test product: HLX14 (proposed denosumab biosimilar) Reference Product: Prolia (EU sourced)	Postmenopausal women with osteoporosis

	Database lock date: July 03, 2024 Study completion date: June 05, 2024 Planned for Inclusion: 478 subjects were planned to be randomised. Enrolled and Randomised: A total of 1078 subjects were screened in the study of which 514 subjects were randomised		Mode of Administration: Subcutaneous injection Dose: 60 mg every 6 months Duration of Treatment: Subjects were administered subcutaneous 60 mg HLX14 or Prolia once every 6 months for up to 18 months (total of 3 doses).	

2.5.5.1. Dose response study(ies)

Not applicable for biosimilars.

2.5.5.2. Main study

Study HLX14-002-PMOP301

This was a randomized, double-blind, international multicenter, parallel-controlled phase III clinical study undertaken to evaluate recombinant anti-RANKL human monoclonal antibody injection (HLX14) versus denosumab injection (Prolia) in postmenopausal women with osteoporosis at high risk of fracture.

The study planned to enrol 478 postmenopausal women with osteoporosis at high risk of fracture and randomized them at 1:1 to either the experiment group (HLX14) or the control group (EU-sourced denosumab [shortened as Prolia hereafter]) based on stratification factors (body mass index [BMI] [< 25, 25-30, > 30] and geographic region [Asian or non-Asian]).

The study included a screening period (28 days), a treatment period 1 (primary endpoint assessment W0 to W52), a treatment period 2 (transition period W52 to W78) and an end-of-study visit (on D547 of the study or premature withdrawal).

The 52-week study design (protocol version 4.0) was discussed with CHMP and documented on 23 June 2022 (EMA/SA/0000084242) and 13 October 2022 (EMA/SA/0000099806). Postmenopausal women at high fracture risk are dosed with 2 doses of HLX14 (60 mg, vial) or EU-Prolia 6 month apart. The primary endpoints were 1) percent change from baseline in BMD at the lumbar spine to week 52

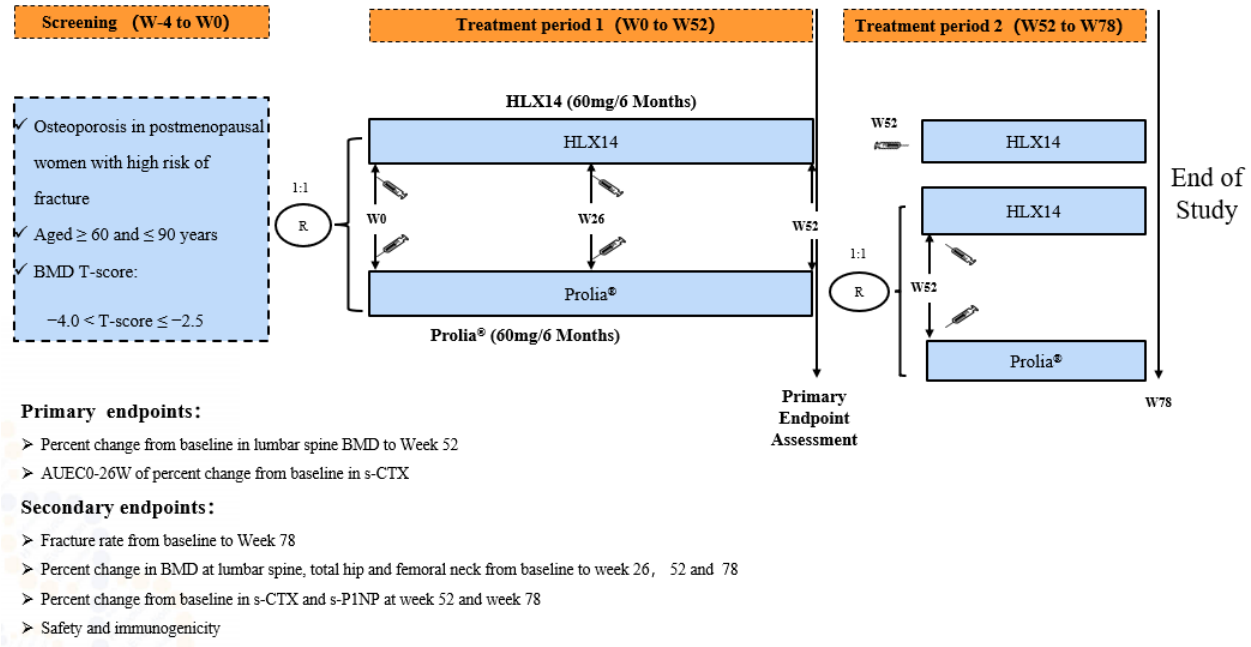
(D365) and 2) Area under the effect-time curve for percent change from baseline of s-CTX from 0 to Week 26 (D183) ($AUEC_{0\text{-}26W}$).

However, FDA requested that a 6 months' single switch after the second dose (the end of the original study design) to be included. Therefore, at Week 52, patients in the EU-Prolia arm are randomized 1:1 to receive either HLX14 (60 mg, vial) or EU-Prolia. Patients in the original HLX14 arm continue their treated with HLX14 (60 mg, vial). All patients receive one additional dose of HLX14 (60 mg, vial) or EU-Prolia. Safety, immunogenicity, PD and secondary efficacy endpoints are assessed up to Week 78.

Per this FDA request, the applicant has revised the study protocol version 4.0 to the current protocol version 5.0. The primary analysis is to be performed after all patients have completed the Week 52 study visit. Final analysis will be performed after all patients have completed the Week 78 study visit.

As the transition period is not considered pivotal for EMA MAA, the applicant proposed to submit Protocol version 4.0, the corresponding Statistical Analysis Plan (SAP), and the CSR per protocol version 4.0 with the data after last patient reaches Week 52. The therapeutic equivalence in terms of improvement percentage in LS-BMD will be conducted if the 95% CI of the difference is contained within the internal (-1.45%, 1.45%), which is reflected in the corresponding SAP and in line with the EMA SA feedback on the design. All efficacy, safety, and immunogenicity data up to Week 52 will be submitted in the initial MAA. Safety update and the additional secondary endpoints assessment up to Week 78 were submitted during the MAA review cycle.

Figure 7. Study schema



Methods

Study participants

The study was conducted in China and Australia, but mainly in China; 41 sites were initiated; subjects were screened and enrolled at 40 sites.

Inclusion criteria

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

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.

Exclusion criteria

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

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:

1) If thyroid stimulating hormone (TSH) level was below local normal range, subject was not eligible for the study;

2) 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;

3) 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 V4.0 protocol Appendix 5).

7. Hepatic diseases:

1) Liver cirrhosis;

2) Unstable liver disease (as defined by the presence of ascites, hepatic encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices or persistent jaundice);

3) Known or Investigator-determined clinically significant biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones and gallbladder polyps);

4) 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);

5) 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 hypocalcemia or hypercalcemia, defined as that albumin-adjusted serum calcium level was not within the normal limit. 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, sodium-dependent glucose transporters 2 (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). 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.

16. Had received denosumab and its biosimilars, or romosozumab and its biosimilars, or cathepsin K inhibitor therapy prior to randomization.

17. Had received the following osteoporosis treatments, or medications that affected bone metabolism or any herbal medications:

1) Use of bisphosphonates (oral or intravenous), fluoride and strontium prior to randomization;

2) Use of parathyroid hormone (PTH) or PTH analogues, such as teriparatide, within 12 months prior to randomization;

3) 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;

4) Use of calcitonin, calcitriol, alfacalcidol or vitamin D analogues within 12 months prior to randomization;

5) 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);

6) 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).

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 • Calcitriol, alfacalcidol and vitamin D analogues	Within 12 months
• 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

18. Subjects with a history or presence of hip fracture or prevalent vertebral fracture (any severe or more than 2 moderate prevalent vertebral fractures).

19. Presence of active healing fracture in the opinion of the Investigator.

20. Subjects at very high risk of fracture who must be treated immediately with an active drug in the opinion of the Investigator.

21. 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.

22. With a history and presence of smoking, except for the following situation:

1) Non-smokers (a history of never smoking > 5 cigarettes/day and not smoking at all for at least the last 2 years prior to screening process);

2) Light smokers (with smoking habit < 5 cigarettes/day, smoking period < 10 years. Light smokers should have not smoked more than 1 cigarette in the week before starting the medical screening process).

23. With a history of drug or alcohol abuse, and with evidence of alcohol or drug abuse within 12 months.

24. 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. Or subjects who had other conditions rendering them unsuitable for inclusion as judged by the Investigator.

Treatments

Treatment period: Subjects received a total of 3 doses of subcutaneous injection of HLX14 or Prolia (once every 6 months (Q6M)).

Treatment period 1: D1-D364, subjects received subcutaneous injection of HLX14 or Prolia 60mg on D1 and D183.

Treatment period 2: D365-D546, on D365, subjects in the Prolia arm were rerandomized 1:1 to either continue with a third dose of Prolia or transition to HLX14 and receive a single dose of HLX14. Subjects in the HLX14 arm continued with a third dose of HLX14.

No dose adjustment was permitted for HLX14 or Prolia. Whenever possible, administration was within the scheduled visits.

Table 9-2 Investigational and Comparator Products

Group name	Experiment group	Control group
Intervention name	HLX14	Denosumab (EU- sourced Prolia®)
Dose formulation	Vial	Syringe (prefilled syringe)
Dose strength	60 mg/1 mL/vial	60 mg/1 mL/syringe
Dosage regimen	60 mg, Q6M	60 mg, Q6M
Route of administration	Subcutaneous injection	Subcutaneous injection
Storage conditions	2-8 °C, away from light, do not freeze or shake)	2-8 °C, away from light, do not freeze or shake)
Packaging and labeling	Study interventions were provided in vials. Each vial was labeled as required per country requirement	Study interventions were provided in prefilled syringes. Each prefilled syringe was labeled as required per country requirement
Batch No.	2203011	1142161 (Ireland) 1149559 (Ireland) 1149181 (Ireland) 1137094B (US) 1139099A (US)
Manufacturer	Shanghai Henlius Biologics Co., Ltd.	Amgen Manufacturing, Limited

Concomitant and rescue therapies

Concomitant therapy required by the protocol

During the treatment period, subjects should be taking at least 1000 mg of calcium daily and at least 400 IU of vitamin D daily until the end of study.

If a subject experienced hypercalcemia during the study, at the discretion of the principal Investigator, calcium and/or vitamin D supplementation was reduced to maintain serum calcium concentration within the normal range. If a subject experienced hypocalcemia during the study, appropriate additional calcium supplementation was administered according to local guidelines to maintain serum calcium concentration within the normal range. If a subject could not tolerate daily calcium or vitamin D supplementation, the formulation was to be changed or the dose was reduced. Intolerance and solutions (i.e., formulation or dose change) were recorded in the subject's eCRF.

Prohibited concomitant medications

The following drugs known or suspected to affect bone metabolism were prohibited during this study, including but not limited to:

Vitamin D analogue (such as active vitamin D 1, 25-dihydroxyvitamin D3, alfacalcidol), vitamin K2, bisphosphonates, fluoride, estrogen-containing contraceptives, hormone replacement therapies (e.g., tibolone, systemic/transdermal/oral estrogen, estrogenic chemicals, etc.), calcitonin, strontium, aluminum, parathyroid hormone or its analogues, glucocorticoids (inhaled or topical glucocorticoids were allowed), and herbal medicines for osteoporosis or affecting bone metabolism.

Objectives

Primary objectives

- 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 pharmacodynamic (PD) endpoint between HLX14 and comparator Prolia in postmenopausal women with osteoporosis at high risk of fracture.

Secondary objectives

- 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.

Outcomes/endpoints

Primary endpoints

• Percent change from baseline in BMD at the lumbar spine to Week 52 (D365) (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 (D183) (AUEC0-26W).

Secondary endpoints

• Percent changes from baseline in BMD at the lumbar spine to Week 26, Week 52, Week 78 (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, and 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, and 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% Rate of 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).

• AEs 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).

Safety

• Incidences of AEs and SAEs, laboratory tests (hematology, serum chemistry, 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.

Sample size

Randomisation and blinding (masking)

The percent change in BMD at lumbar spine from baseline to Week 52 (D365) and AUEC of percent change of s-CTX from baseline to Week 26 (D183) were set as the co-primary endpoints to confirm the similarity of clinical efficacy and PD between HLX14 and Prolia in this study. The equivalence conclusion could only be drawn when both endpoints are met.

According to the previously published meta-analysis results, the difference between Prolia and placebo in percent change in BMD from baseline in the proposed trial population was 5.35% (95% CI: 4.83%,

5.87%). A clinical equivalence margin of ±1.45% would retain 70% of the treatment effect of Prolia (lower 95% CI limit), as determined by a two one-sided test α of 0.025.

Referring to a previous study (Bone HG, 2008) the percent change of BMD from baseline between denosumab and placebo at 24 months was 6.5% (95% CI: 5.8%, 7.2%), with a standard deviation of 4.56% estimated based on the normal distribution confidence interval estimation formula: (100 [1-α])%, confidence interval: ($\mu - Z\alpha/2 * SE, \mu + Z\alpha/2 * SE$). With a 1:1 ratio for the randomization between HLX14 and Prolia groups, a two one-sided α of 0.025 and a standard deviation of approximately 4.56%, a minimum of 215 evaluable subjects per group were required to obtain 81.5% power when applying the above equivalence margin in this study.

For AUEC of s-CTX percent change, the coefficient of variation (CV) for AUEC was approximately 20% based on the study result from 24 subjects in part I, phase I of the study. By assuming the geometric mean ratio of HLX14 AUEC to Prolia AUEC as 0.95, significance level as α = 0.025 (two one-sided tests), and the equivalence interval for s-CTX percent change AUEC as 80%-125%, a > 99% power was obtained with a sample size of 430.

In summary, a total of 478 subjects (239 each in the HLX14 and Prolia groups) were planned to be enrolled in this study, taking into consideration of a dropout rate of 10%.

The sample size and power for this study were calculated by PASS (15.0.12).

Statistical methods

Analysis set

• Intention-to-treat (ITT) set: Defined as all postmenopausal women with osteoporosis at high risk of fracture who were randomized in this study.

• Per protocol set (PPS): PPS was a subset of ITT set, and PPS was consisted of all subjects randomized without major protocol deviations that significantly affected the primary efficacy assessment. The specific definition of PPS was confirmed before database lock. As a supportive analysis, the analysis based on the PPS complemented the analysis based on the ITT set.

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

• Pharmacodynamic set (PDS): All subjects who were randomized to receive at least one dose of study drug and had at least one post-administration PD concentration at the planned PD sample collection time point without significant protocol violation or deviation from the evaluation of the s-CTX AUEC0-26W. PDS was used for statistical analysis of PD indicators.

• Pharmacokinetic set (PKS): Defined as all randomized subjects who received at least one dose of HLX14 or Prolia and had at least one post-dose serum concentration at a scheduled sampling time point, without protocol deviations that could significantly affect the PK profile of the study drug.

Efficacy analyses

Primary efficacy endpoint

The primary endpoint of this study was percent change from baseline in BMD (BMD changes %) at the lumbar spine to Week 52 (D365). Percent change from baseline in BMD(%) = (BMD at Week 52 - BMD at Baseline BMD at Baseline)×100

Based on the ITT set, using the imputed dataset, the analysis model for % BMD change was a linear regression (ANCOVA) of % BMD change with the treatment group as a fixed effect and stratification factors BMI (< 25, 25-30, > 30), and baseline BMD values as covariates. Adjusted means of % BMD change in the two groups with standard error and the difference between the two groups with two-sided 95% CIs were calculated.

ICEs that occurred after treatment initiation and either precluded observation of the variable or affect its interpretation used a hypothetical strategy to estimate a treatment effect as if all subjects adhered to treatment until the primary analysis time point.

For subjects with lumbar spine fractures, treatment strategy is applied, continue to data collection and analysis. For lumbar spine fractures that occur early, such as within 30 days after the first dose, the occurrence of fractures can be considered independent of efficacy, and the missing value is multiple imputed under MAR assumption. For lumbar spine fractures that occur at other times (treated related fractures), the missing value is imputed by the worst value collected before the ice happened.

Handling of missing data for the primary efficacy estimand

Imputation: datasets were generated, using seed number , missing data at Week 26 was first imputed using the regression imputation model with baseline BMD and BMD from Week 26, baseline BMI (kg/m2) (<25, 25-30, >30) as terms in the model, by treatment group.

Repeat for scheduled week 52 sequentially, subjects whose missing data were imputed for previous weeks contributed to the imputation for the current week.

Analysis: Analysis of each of the complete data sets, using the analysis models (ANCOVA) .

Pooling: Combine the results of all ANCOVA models using Rubin's rules with the SAS PROC MI ANALYZE procedure.

For those subjects discontinuing due to either AE, lack of efficacy or treatment related lumbar spine fracture, imputation was treated differently. The imputed Week 26/Week 52 values (after following the steps above) would be adjusted and therefore ascribed an extreme unfavorable value. Use worst-observation-carried forward (WOCF) to impute missing data at Week 26 and Week 52. The worst (lowest) observed BMD value which was selected in the observed values after hypothetical strategy was applied (including the baseline value) would be used for the missing data imputation.

Sensitivity analyses

Table 9-6 Sensitivity Analysis

#	Sensitivity Analysis	Detail description
1	**Mixed-effect model for repeated measures (MMRM)**	The same strategy to handle the ICEs with the primary analysis, and for those patients discontinuing due to either AE or to lack of efficacy and treatment related lumbar spine fracture, missing data was imputed by WOCF. Use **mixed-effect model for repeated measures (MMRM)**, treatment group, visit and visit by treatment group interaction were used as the fixed effects, and the stratification factors of BMI (< 25, 25-30, > 30),

		and the baseline BMD values were used as covariates, to calculate the adjusted means of the percentage changes from baseline in two groups, with standard error, and the difference between the two groups with 2-sided 95% CI. An unstructured covariance matrix was used to model the covariance structure.
2	**Tipping point analysis**	Tipping-point multiple imputation analysis: in this sensitivity analysis, missing data were first imputed based on MAR like the primary analysis. Secondly, for each group a penalty was added to the imputed values at week 52 where ICEs (premature treatment discontinuation before week 26 due to any reason, use of prohibited drugs and treatment related lumbar spine fractures) happened. The approach was to gradually increase this penalty until the BMD conclusion from the primary analysis was changed. The specific value of the penalty that changes the conclusion was used to evaluate the robustness of the primary analysis result. This sensitivity analysis was used for evaluating the robustness of the conclusions. The penalty δ would start at 0 and increase or decrease by an appropriate value (%) at each imputation until upper boundary of the 2-sided 95% CI for the adjusted mean difference was > 1.45% or lower boundary < -1.45%. Least square mean difference between treatment group and their associated 95% CIs were provided for each penalty level.
3	**Treatment policy**	All ICEs applied treatment policy, the week 52 data collected after ICE occurrence was used. MMRM model was used.
4	**Using BMD measurement from the Investigator/site**	BMD measurements from the Investigator/site were recorded in EDC. The same strategy to handle the ICEs with the primary analysis, and for those patients discontinuing due to either AE or to lack of efficacy and treatment related fracture, missing data is imputed by WOCF. MMRM model was used.
5	**Add covariate**	The same strategy to handle the ICEs with the primary analysis, and for those patients discontinuing due to either AE or to lack of efficacy and treatment related fracture, missing data was imputed by WOCF. Added age (<65 years,>=65 years) and prior bisphosphonate use (yes/no) in the multiple imputation and ANCOVA. Also presented the results of using treatment policy strategy and MMRM model adding covariates.

Supplementary analysis

Supplementary analysis: Based on the PPS, and the actual treatment the subject received, the same strategy to handle the ICEs and missing data with the primary analysis.

Secondary efficacy endpoints

- Fracture rate from baseline to Week 52

Fracture rate from baseline to Week 52 = (number of subjects with new fractures from baseline to week 52/total number of subjects) × 100%

Handling of remaining intercurrent events:

#	Intercurrent events	Intercurrent events sub-category	Strategy
1	Premature treatment discontinuation before week 26	1.1 Treatment discontinuation due to adverse event (Related to treatment)	**Hypothesis strategy:** data collected after ICE occurred will not be used for analysis. hypothesis that the ICE did not occur.
		1.2 Treatment discontinuation due to lack of efficacy (Related to treatment)	
		1.3 Treatment discontinuation for other reasons. (Not related to treatment)	
2	Bone-affecting interventions	2.1 Use of prohibited drugs	
		2.2 Non-drug intervention(including but not limited to bilateral oophorectomy)	
3	AE's affecting bone	3.1 Injury, poisoning and procedural complications: spinal fracture,hip fracture and so on	Fracture is the target endpoint
		3.2 Metabolism and nutrition disorders/Endocrine disorders: diabetes mellitus(new-onset),hyperthyroidism and so on	**Hypothesis strategy:** data collected after ICE occurred will not be used for analysis. hypothesis that the ICE did not occur.
		3.3 Gastrointestinal disorders: Crohn's disease ,ulcerative colitis and son on	
		3.4 Musculoskeletal and connective tissue disorders: Rheumatoid arthritis ,ankylosing spondylitis and so on	
		3.5 Nervous system disorders: Parkinson's disease,spinal cord injury and so on	
		3.6 Other: Chronic obstructive pulmonary disease ,HIV infection and so on	
4	Changes in concomitant medication	Changes in concomitant medication:thiazolidinedione,GLP-1 and so on	

Based on ITT, hypothetical strategy is applied as above. Fracture rate was analyzed using the Cochran-Mantel-Haenszel (CMH) test to compare the two treatment groups. The strata for the test were those used for stratified randomization (BMI [< 25, 25-30, > 30]). The relative risk/risk difference between two groups and its 95% CI were estimated.

Sensitivity analysis 1: Fracture rate was analyzed without considering stratification factors.

Sensitivity analysis 2: For ICE 1.1 and 1.2, used "fracture occurs" imputation.

Sensitivity analysis 3: All ICEs applied treatment policy; the week 52 data collected after ICE occurrence were used.

Supplementary analysis: Based on the PPS.

- Other secondary efficacy endpoints

Other secondary efficacy endpoints: percent change in BMD at the lumbar spine from baseline to Week 26 (D183), percent changes in BMD at total hip from baseline to Week 26 (D183) and Week 52 (D365) and percent changes in BMD at the femoral neck from baseline to Week 26 (D183) and Week 52 (D365) were analyzed by mixed-effect model for repeated measures (MMRM). The treatment group,

visit and visit by treatment group interaction were used as the fixed effects, and the stratification factors of BMI (< 25, 25-30, > 30), and the baseline values for corresponding measures were used as covariates, an unstructured covariance matrix was used to calculate the adjusted means of the changes from baseline (or percentage) in these groups, with standard error and the difference between the two groups with two-sided 95% CIs. Hypothetical strategy was applied the same as with the primary endpoint analysis.

Handling of remaining intercurrent events:

#	Intercurrent events	Intercurrent events sub-category	Strategy
1	Premature treatment discontinuation before week 26	1.1 Treatment discontinuation due to adverse event (Related to treatment)	**Hypothesis strategy:** data collected after ICE occurred will not be used for analysis. hypothesis that the ICE did not occur. outcomes are predicted on the basis of similar patients.
		1.2 Treatment discontinuation due to lack of efficacy (Related to treatment)	
		1.3 Treatment discontinuation for other reasons. (Not related to treatment)	
2	Bone-affecting interventions	2.1 Use of prohibited drugs	
		2.2 Non-drug intervention(including but not limited to bilateral oophorectomy)	
3	AE's affecting bone	3.1 Injury, poisoning and procedural complications: spinal fracture,hip fracture and so on	For **lumbar spine BMD endpoint** ,if patients with new lumbar spine fracture, use Treatment Policy: continue to collect data, the collected week 52 data will be used for analysis. For **total hip/ femoral neck BMD endpoints** , if patients with total hip or femoral neck fracture, apply hypothesis strategy: data collected after ICE occurred will not be used for analysis. hypothesis that the ICE did not occur. outcomes are predicted on the basis of similar patients.

		3.2 Metabolism and nutrition disorders/Endocrine disorders: diabetes mellitus(new-onset),hyperthyroidism	**Hypothesis strategy:** data collected after ICE occurred will not be used for analysis. hypothesis that the ICE did not occur. outcomes are predicted on the basis of similar patients.
		3.3 Gastrointestinal disorders: Crohn's disease ,ulcerative colitis and son on	
		3.4 Musculoskeletal and connective tissue disorders: Rheumatoid arthritis ,ankylosing spondylitis and so	
		3.5 Nervous system disorders: Parkinson's disease,spinal cord injury and so on	
		3.6 Other: Chronic obstructive pulmonary disease ,HIV infection and	
4	Changes in concomitant medication	Changes in concomitant medication:thiazolidinedione,GLP-1 and so on	

For total hip or femoral neck BMD, if the postbaseline measurements are inconsistent with the baseline measurements, postbaseline measurements will not be included in the analysis.

Sensitivity analysis 1: All ICEs applied treatment policy, BMD data collected after the ICE occurrence were used, also used MMRM on MAR assumption.

Sensitivity analysis 2: Using BMD measurement from the Investigator/site.

Supplementary analysis: Based on the PPS.

Pharmacodynamic analyses

Primary pharmacodynamic endpoint

The primary PD endpoint of this study was area under the effect-time curve for percent change of s-CTX from baseline to Week 26 (D183) (AUEC0-26W).

Based on the PDS, the PD parameter AUEC0-26W for s-CTX was calculated based on the actual sampling timepoint by WinNonLin version 8.2 with a non-compartment model (NCA). The AUEC of baseline corrected serum CTX concentrations (% change from baseline) was calculated using the linear trapezoidal method. s-CTX concentration data below the lower limit of quantification were treated as 1/2 LLOQ when calculating the PD parameter. Furthermore, descriptive statistics were summarized, including the number of subjects, arithmetic mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, and geometric coefficient of variation. The between-group least squares means (LSMs), geometric mean ratio (GMRs), and its 95% CI for AUEC0-26W were calculated by ANOVA. The factor in the ANOVA was the treatment groups. The equivalence of between-group s-CTX PD parameter AUEC0-26W could be demonstrated when the 95% CI of GMR for AUEC0-26W fall within the equivalence interval (0.80 to 1.25).

If necessary, a stratification analysis was performed for the primary PD endpoint AUEC0-26W based on the immunogenicity results.

Supplementary analysis

Supplementary analysis 1: Based on the ITT, all ICEs applied treatment policy, the concentration data collected after ICE occurrence was used. Missing data was not imputed. Analysis method was the same with primary PD analysis.

Supplementary analysis 2: Based on the PDS, excluding patients with W0-26 ICEs which major affecting AUEC0-26w, that was patients with W0-26 ICEs (bone-affecting interventions, adverse events affecting bone, and changes in concomitant medication) and patent's AUEC0-26W deviation from the mean AUEC0-26W of all subjects were greater than 20%. Analysis method was the same with primary PD analysis.

Supplementary analysis 3: Based on the PDS, patients with W0-26 ICEs or not meeting with Inclusion and Exclusion Criteria and leading to be excluded from PPS, these patients were excluded from supplementary analysis. Analysis method was the same with primary PD analysis.

Secondary pharmacodynamic endpoints

Repeatedly measured continuous variables including s-CTX and s-P1NP in secondary PD measures were analyzed using a mixed-effect model for repeated measurement (MMRM). The treatment group, visit and visit by treatment group interaction were used as the fixed effects, and the stratification factors of BMI (< 25, 25-30, > 30), and the baseline values for corresponding measures were used as covariates, an unstructured covariance matrix was used to calculate the adjusted means of the changes from baseline (or percentage) in these groups, with standard error.

Pharmacokinetic analyses

The analysis of PK was performed based on PKS.

Serum concentrations of HLX14 and Prolia were summarized at nominal sample time according to treatment group by the number of below the limit of quantification (BLQ), number of observations, maximum, median, minimum, standard deviation, arithmetic mean, geometric mean (geomean), CV, and geometric CV (CVb%).

A scatter diagram was plotted using linear and semi-logarithmic scales for the arithmetic mean and SD of PK concentrations by treatment group, respectively.

Subject PK concentrations were listed based on the PKS.

Immunogenicity analyses

Based on the SS, ADA and NAb were summarized by treatment group and scheduled study visit. The proportion of subjects with at least one positive result of ADA/NAb after administration of the study drug in each group was summarized separately. If necessary, a stratification analysis would be performed for PK, PD, efficacy, and AE based on the immunogenicity results.

Safety analyses

All safety analyses were performed based on the SS.

Based on the SS, the number and incidence of treatment emergent adverse events (TEAEs) in each treatment group were summarized by system organ class (SOC) and preferred term (PT), and the common terminology criteria for adverse events (CTCAE) grade were summarized. In addition, serious TEAEs, severe TEAEs (Grade 3, 4, and 5), adverse event of special interest (AESIs), HLX14/Prolia-related TEAEs, HLX14/Prolia-related serious TEAEs, TEAEs leading to HLX14/Prolia discontinuation, TEAEs leading to HLX14/Prolia interruption were summarized accordingly.

For clinical laboratory tests, physical examinations, vital signs, and 12-lead ECG, shift tables of changes from baseline in clinical evaluation (normal, abnormal with no clinical significance, abnormal

with clinical significance or missing) were presented at each protocol scheduled study visit by treatment group.

Subgroup analyses

Based on the ITT set, all primary efficacy endpoint and secondary efficacy endpoints were summarized for the following subgroups:

· Age (< 60, ≥ 60 and ≤ 85, > 85).

· Age (< 65, ≥ 65).

• BMI (< 25, 25 – 30, > 30).

• Geographic region (Asian or non-Asian).

• Prior use of bisphosphonates (Y, N).

• Smokers (non-smokers, light smokers, other).

Categories including less than 5% ITT subjects might be collapsed. Only descriptive analysis of subgroups might not be provided.

Results

Participant flow

A total of 1078 subjects were screened, and 564 subjects failed screening. A total of 514 subjects were randomized to the HLX14 group (256 subjects) or the Prolia group (258 subjects), and all the randomized subjects received the study treatments.

Among the randomized subjects, 471 (91.6%) subjects (HLX14 group vs. Prolia group: 234 [91.4%] vs. 237 [91.9%]) completed the treatment of Week 26, and 43 (8.4%) subjects (22 [8.6%] vs. 21 [8.1%]) discontinued the treatment before Week 26. The most common reason for treatment discontinuation was withdrawal of informed consent (10 [3.9%] vs. 11 [4.3%]). Other reasons for treatment discontinuation were subject decision (7 [2.7%] vs. 9 [3.5%]), poor compliance (3 [1.2%] vs. 0), lost to follow-up (2 [0.8%] vs. 0), and adverse event (0 vs. 1 [0.4%]).

A total of 478 (93.0%) subjects (236 [92.2%] vs. 242 [93.8%]) completed the study visit of Week 52, and 36 (7.0%) subjects (20 [7.8%] vs. 16 [6.2%]) discontinued from the study visit before Week 52. The most common reason for study discontinuation before Week 52 was withdrawal of informed consent (11 [4.3%] vs. 11 [4.3%]). Other reasons for study discontinuation were subject decision (5 [2.0%] vs. 3 [1.2%]), poor compliance and failed to attend follow-up in time (2 [0.8%] vs. 1 [0.4%]), lost to follow-up (2 [0.8%] vs. 0), and adverse event (0 vs. 1 [0.4%]).

Treatment period 2

On D365, 220 subjects from the Prolia group were re-randomized to the Prolia/HLX14 group (110 subjects) and the Prolia/Prolia group (110 subjects), 220 subjects in the HLX14 group continued into the HLX14/HLX14 group without re-randomization; and all 440 subjects received the third dose of study treatment (subjects in the HLX14/HLX14 group and the Prolia/HLX14 group received a single dose of HLX14; subjects in the Prolia/Prolia group received a single dose of Prolia). A total of 435 subjects in the three groups (HLX14/HLX14 group vs. Prolia/HLX14 group vs. Prolia/Prolia group: 219 [99.5%] vs. 108 [98.2%] vs. 108 [98.2%]) completed the study visit of Week 78. One (0.5%) subject in the HLX14/HLX14 group discontinued the study visit before Week 78 due to poor compliance and

failed to attend follow-up in time; 2 (1.8%) subjects in the Prolia/HLX14 group discontinued the study visit before Week 78 due to poor compliance and failed to attend follow-up in time and subject decision, respectively; 2 (1.8%) subjects in the Prolia/Prolia group discontinued the study visit before Week 78 due to withdrawal of inform consent and subject decision, respectively.

A total of 74 of the 514 subjects did not receive the Week 52 treatment of study drug (HLX14/Not treated: 36 subjects; Prolia/Not treated: 38 subjects). A total of 21 subjects in the two groups (HLX14/Not treated vs. Prolia/Not treated: 11 [30.6%] vs. 10 [26.3%]) completed the study treatment, and 53 subjects in the two groups (25 [69.4%] vs. 28 [73.7%]) discontinued the study treatment. The most common reason for treatment discontinuation was withdrawal of informed consent (11 [30.6%] vs. 13 [34.2%]). Other reasons for treatment discontinuation were subject decision (9 [25.0%] vs. 10 [26.3%]), poor compliance (3 [8.3%] vs. 1 [2.6%]), lost to follow up (2 [5.6%] vs. 0), adverse event (0 vs. 3 [7.9%]), and physician decision (0 vs. 1 [2.6%]). A total of 30 subjects in the two groups (HLX14/Not treated vs. Prolia/Not treated: 16 [44.4%] vs. 14 [36.8%]) completed the study, and 44 subjects in the two groups (20 [55.6%] vs. 24 [63.2%]) discontinued the study. The most common reason for study discontinuation was withdrawal of informed consent (11 [30.6%] vs. 14 [36.8%]). Other reasons for study discontinuation were subject decision (5 [13.9%] vs. 5 [13.2%]), poor compliance and failed to attend follow-up in time (2 [5.6%] vs. 1 [2.6%]), lost to follow-up (2 [5.6%] vs. 0), adverse event (0 vs. 3 [7.9%]) and physician decision (0 vs. 1 [2.6%]).

Subject disposition

Table 10-1 Subject Disposition (All screened subjects)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects screened			1078
Screen failure			564
Randomization[1], n (%)	256 (100)	258 (100)	514 (100)
Subjects treated[1], n (%)	256 (100)	258 (100)	514 (100)
Subjects not treated, n (%)	0	0	0
Completed week 26 treatment[2], n (%)	234 (91.4)	237 (91.9)	471 (91.6)
Discontinued from treatment before week 26[2], n (%)	22 (8.6)	21 (8.1)	43 (8.4)
Reason for discontinuation, n (%)			
Adverse Event	0	1 (0.4)	1 (0.2)
Lack of Efficacy	0	0	0
Withdrawal of Inform Consent	10 (3.9)	11 (4.3)	21 (4.1)
Lost to Follow-up	2 (0.8)	0	2 (0.4)
Death	0	0	0
Physician Decision	0	0	0
Poor Compliance	3 (1.2)	0	3 (0.6)
Serious Protocol Violation	0	0	0
Subject Decision	7 (2.7)	9 (3.5)	16 (3.1)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Other	0	0	0
Completed study on week 52[3], n (%)	235 (91.8)	242 (93.8)	477 (92.8)
Discontinued from study before week 52, n (%)	20 (7.8)	16 (6.2)	36 (7.0)
Reason for discontinuation, n (%)			
Withdrawal of Inform Consent	11 (4.3)	11 (4.3)	22 (4.3)
Adverse Event	0	1 (0.4)	1 (0.2)
Lack of Efficacy	0	0	0
Lost to Follow-up	2 (0.8)	0	2 (0.4)
Death	0	0	0
Physician Decision	0	0	0
Poor Compliance and Fails to Attend Follow-up in Time	2 (0.8)	1 (0.4)	3 (0.6)
Serious Protocol Violation	0	0	0
Study Terminated by Regulatory Authorities	0	0	0
Study Terminated by Sponsor	0	0	0
Subject Decision	5 (2.0)	3 (1.2)	8 (1.6)
Other	0	0	0

N: The number of subjects randomized; n: The number of subjects in specific category; %: (n/N*100).

[1] Stratified block randomization was used to randomize the eligible subjects to the experiment group (HLX14) or the control group (Prolia®) at 1:1 based on stratification factors BMI (< 25, 25-30, > 30) and geographic region (Asian or non-Asian). Subjects received subcutaneous injection of HLX14 or Prolia® 60 mg on D1 and D183.

[2] Completed week 26 Treatment means subjects completed week 26 dose. Discontinued from treatment before week 26 summaries subjects who did not complete week 26 dose.

[3] Completed study on week 52 means subjects completed visit week 52.

Data source: Table 14.1.1.1.

Table 14.1.2.1.1
Major Protocol Deviations
(Intention-to-Treat Set)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects with at least one major protocol deviation, n (%)[1]	130 (50.8)	118 (45.7)	248 (48.2)
Classification of major protocol deviations, n (%)[1]	130 (50.8)	118 (45.7)	248 (48.2)
AE/SAE	0	0	0
Disallowed Medications	16 (6.3)	11 (4.3)	27 (5.3)
Informed Consent	0	0	0
Inc/Excl Criteria	32 (12.5)	22 (8.5)	54 (10.5)
IP Admin/Study Treat	13 (5.1)	10 (3.9)	23 (4.5)
Procedures/Tests	21 (8.2)	17 (6.6)	38 (7.4)
Visit Schedule	94 (36.7)	98 (38.0)	192 (37.4)
Withdrawal Criteria	0	0	0
Other	0	0	0

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
[1] If a subject had multiple PDs, the subject was counted only once.
Source: Listing 16.2.2.1
[Source: t addv.sas] 22MAR2024T2:30:49 EDC DATE: 19JAN2024T10:44:00

Table 14.1.2.1.2
Major Protocol Deviations Related to COVID 19
(Intention-to-Treat Set)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects with at least one major protocol deviation related to COVID 19, n (%)[1]	47 (18.4)	49 (19.0)	96 (18.7)
Classification of major protocol deviations, n (%)[1]	47 (18.4)	49 (19.0)	96 (18.7)
AE/SAE	0	0	0
Disallowed Medications	0	0	0
Informed Consent	0	0	0
Inc/Excl Criteria	0	0	0
IP Admin/Study Treat	2 (0.8)	1 (0.4)	3 (0.6)
Procedures/Tests	3 (1.2)	1 (0.4)	4 (0.8)
Visit Schedule	42 (16.4)	48 (18.6)	90 (17.5)
Withdrawal Criteria	0	0	0
Other	0	0	0

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
[1] If a subject had multiple PDs, the subject was counted only once.
Source: Listing 16.2.2.1
[Source: t addv.sas] 22MAR2024T2:30:50 EDC DATE: 19JAN2024T10:44:00

Table 10-2 Important Protocol Deviations (Intention-To-Treat set)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects with at least one important protocol deviation, n (%)[1]	21 (8.2)	15 (5.8)	36 (7.0)
Classification of important protocol deviations, n (%)[1]	21 (8.2)	15 (5.8)	36 (7.0)
AE/SAE	0	0	0
Disallowed Medications	8 (3.1)	4 (1.6)	12 (2.3)
Informed Consent	0	0	0
Inc/Excl Criteria	2 (0.8)	0	2 (0.4)
IP Admin/Study Treat	8 (3.1)	3 (1.2)	11 (2.1)
Procedures/Tests	0	0	0
Visit Schedule	5 (2.0)	9 (3.5)	14 (2.7)
Withdrawal Criteria	0	0	0
Other	0	0	0

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
Important PDs were the protocol deviations that significantly affected the primary efficacy assessment and leading subjects excluded from PPS.
[1] If a subject had multiple PDs, the subject was counted only once.
Data source: Table 14.1.2.1.3.

Conduct of the study

The original protocol, HLX14-002-PMOP301 V1.0, dated 10 Sep 2021, was amended 4 times during the conduct of this study (V2.0, V3.0, V4.0, V5.0). This study report presents the results based on V4.0 of the protocol. Major changes in amendments specific to the study are summarized below.

Scientific advice was provided on 23 June 2022 (EMA/SA/0000084242) and on 13 October 2022 (EMA/SA/0000099806).

Major changes from version 1.0 (10 Sep 2021) to 2.0 (15 Mar 2022):

• Followed the requirements of E9 (R1), added descriptions of estimands and ICEs, etc.

• The trial for reference medicine showed that denosumab had a therapeutic efficacy on postmenopausal osteoporosis, and BMD increased within 1 year. As a similar drug, the same indications and BMD at 1 year were selected as endpoints.

• Specified that the subjects must first meet the diagnosis of postmenopausal osteoporosis.

• Added the exclusion of causes of secondary osteoporosis.

• Added new sections to allow repeated testing during the screening period, and allowed screening failures to be rescreened at the discretion of the Investigator.

• Added the time window for administration (±2 weeks).

• Added treatment requirements for vitamin D and calcium tablets.

• Described emergency unblinding in detail.

• Adjusted the visit time window to ±7 days; the relevant testing time window at the end-of-study visit was 14 days.

• Changed causality from quintile to dichotomy.

• Specified that no interim analysis was performed.

Major changes from version 2.0 (15 Mar 2022) to 3.0 (18 Jul 2022):

• Updated and defined statistical analysis and ICEs.

• Added primary endpoint (PD) as per EMA requirements: s-CTX AUEC0-26W assessment.

• Added secondary efficacy endpoints of fracture rate at Week 52 and BMD percent changes at lumbar spine, total hip, femoral neck at Week 26 as per EMA requirements.

• Set s-CTX and s-P1NP as secondary PD indicators for analysis; consistent with the sampling points for primary PD indicators, conducted comparison for the added time points using percentage changes.

• Changed the dosage of Vitamin D to at least 400 IU/day.

• Changed the lower age limit to 60 years as per EMA requirements.

• Removed additional high risks based on FDA and EMA comments.

• Specified that imaging results should be based on central imaging findings for confirmation.

• Clearly stated that patients with hepatitis C RNA positive could not be enrolled.

· Clearly stated that indirect bilirubin ≥ 1.5 × ULN was allowed when direct bilirubin was < 35% total bilirubin.

• Added ADA testing on D15 and D57 as per EMA recommendation. Added D15 sampling points as there was a high likelihood of ADA development at early treatment stage while adding D57 to ensure appropriate sampling frequency to identify the presence of transient ADA positivity.

• Adjusted the cut-off value to 1.45% to recalculate the sample size; calculated the sample size according to the AUEC equivalent interval of 80-125%.

Major changes from version 3.0 (18 Jul 2022) to 4.0 (02 Nov 2022):

• Added other analyses of ICEs and provide explanation.

• Updated the prohibited concomitant medications and duration of prohibition according to EMA's feedback.

• Added the exclusion criteria of smoking and clarified the definition of light smokers.

• Updated unplanned sampling points based on the evaluation of the potential impact of immunogenicity/PK results on safety, as well as feedback from EMA.

• Updated significance level for primary PD endpoint.

• Updated missing values imputation rule according to EMA & CDE's advice.

• Added supplementary analysis according to EMA's advice.

• Updated statistical analysis method for fracture rate as the formula was updated.

• Specified that "percent changes in BMD at the lumbar spine from baseline to Week 26 (D183)" were analyzed in MMRM together with Week 52.

• Updated the request of emergency unblinding.

• Clarified the prohibited concomitant therapy.

Baseline data

Treatment period 1

Table 11-2 Demographic Characteristics (Intention-To-Treat set)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Age (years)			
n	256	258	514
Mean (SD)	66.9 (5.89)	67.0 (5.80)	67.0 (5.84)
Median (Min, Max)	67.0 (52, 87)	67.0 (51, 86)	67.0 (51, 87)
Age Category (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 Category (years), n (%)			
< 65	81 (31.6)	83 (32.2)	164 (31.9)
≥ 65	175 (68.4)	175 (67.8)	350 (68.1)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	255 (99.6)	257 (99.6)	512 (99.6)
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	1 (0.4)	1 (0.4)	2 (0.4)
Other	0	0	0
Ethnic Group, 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)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Unknown	0	0	0
Region, n (%)[1]			
Asian	255 (99.6)	257 (99.6)	512 (99.6)
Non-Asian	1 (0.4)	1 (0.4)	2 (0.4)
Height (cm)			
n	256	258	514
Mean (SD)	154.80 (5.648)	154.77 (5.553)	154.79 (5.595)
Median (Min, Max)	155.00 (137.4, 168)	155.00 (135.7, 174.5)	155.00 (135.7, 174.5)
Weight (kg)			
n	256	258	514
Mean (SD)	55.78 (7.305)	55.94 (7.722)	55.86 (7.510)
Median (Min, Max)	56.00 (35.5, 77.5)	55.95 (36, 77.8)	56.00 (35.5, 77.8)
BMI (kg/m^2)			
n	256	258	514
Mean (SD)	23.29 (2.904)	23.35 (2.981)	23.32 (2.940)
Median (Min, Max)	23.48 (14.2, 32.3)	23.22 (14.6, 31.4)	23.33 (14.2, 32.3)
BMI Category (kg/m^2), n (%)[1]			
< 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)
Smoking Status, n (%)			
Never	253 (98.8)	252 (97.7)	505 (98.2)
Former	2 (0.8)	2 (0.8)	4 (0.8)
Current	1 (0.4)	4 (1.6)	5 (1.0)
Classification of Smoker, n (%)			
Non-smokers	253 (98.8)	252 (97.7)	505 (98.2)
Light smokers	2 (0.8)	3 (1.2)	5 (1.0)
Other	1 (0.4)	3 (1.2)	4 (0.8)
Drink Status, n (%)			
Never	250 (97.7)	254 (98.4)	504 (98.1)
Former	3 (1.2)	1 (0.4)	4 (0.8)
Current	3 (1.2)	3 (1.2)	6 (1.2)
Alcohol Abusers, n (%)			
Yes	0	0	0
No	256 (100)	258 (100)	514 (100)
History of Medicine Allergies, n (%)			
Yes	19 (7.4)	11 (4.3)	30 (5.8)
No	237 (92.6)	247 (95.7)	484 (94.2)
Any Other Allergic History, n (%)			
Yes	4 (1.6)	7 (2.7)	11 (2.1)
No	252 (98.4)	251 (97.3)	503 (97.9)
Any Family History of Hip Fracture, n (%)			
Yes	16 (6.3)	23 (8.9)	39 (7.6)
No	240 (93.8)	235 (91.1)	475 (92.4)
Prior Use of Bisphosphonates, n (%)			
Yes	11 (4.3)	8 (3.1)	19 (3.7)
No	245 (95.7)	250 (96.9)	495 (96.3)

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100)
BMI = Body Mass Index, BMI = Weight (kg) / Height $(m)^2$.
[1] Randomization stratification from IWRS.
Data source: Table 14.1.4.1.1.

Table 14.1.4.1.3
Baseline Characteristics
(Intention-to-Treat Set)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
BMD at lumbar spine by central image (g/cm^2)			
n	256	258	514
Mean (SD)	0.7365 (0.0793)	0.7394 (0.0793)	0.7379 (0.0792)
Median (Min, Max)	0.7345 (0.485, 0.907)	0.7325 (0.542, 0.916)	0.7330 (0.485, 0.916)
BMD at total hip by central image (g/cm^2)			
n	256	258	514
Mean (SD)	0.7051 (0.0915)	0.7019 (0.0931)	0.7035 (0.0923)
Median (Min, Max)	0.7005 (0.464, 1.005)	0.7005 (0.466, 1.002)	0.7005 (0.464, 1.005)
BMD at femoral neck by central image (g/cm^2)			
n	256	258	514
Mean (SD)	0.6136 (0.1014)	0.6141 (0.1021)	0.6138 (0.1017)
Median (Min, Max)	0.5975 (0.357, 0.965)	0.6050 (0.361, 0.932)	0.6025 (0.357, 0.965)
T-score at lumbar spine by central image			
n	256	258	514
Mean (SD)	-3.210 (0.5925)	-3.208 (0.5414)	-3.209 (0.5669)
Median (Min, Max)	-3.140 (-5.11, -1.27)	-3.175 (-4.9, -1.9)	-3.150 (-5.11, -1.27)
BMD at lumbar spine by investigator (g/cm^2)			
n	256	258	514
Mean (SD)	0.7376 (0.0816)	0.7398 (0.0818)	0.7387 (0.0817)
Median (Min, Max)	0.7355 (0.515, 1.069)	0.7335 (0.533, 0.979)	0.7345 (0.515, 1.069)
BMD at total hip by investigator (g/cm^2)			
n	256	258	514
Mean (SD)	0.7087 (0.0923)	0.7076 (0.0946)	0.7081 (0.0934)
Median (Min, Max)	0.6995 (0.429, 0.982)	0.7090 (0.481, 0.994)	0.7030 (0.429, 0.994)
BMD at femoral neck by investigator (g/cm^2)			

Table 14.1.4.1.3
Baseline Characteristics
(Intention-to-Treat Set)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
n	256	258	514
Mean (SD)	0.6129 (0.0987)	0.6154 (0.1006)	0.6142 (0.0996)
Median (Min, Max)	0.6015 (0.328, 0.945)	0.6100 (0.355, 0.931)	0.6050 (0.328, 0.945)
T-score at lumbar spine by investigator			
n	256	258	514
Mean (SD)	-3.103 (0.6016)	-3.109 (0.6219)	-3.106 (0.6113)
Median (Min, Max)	-3.000 (-5.1, -0.4)	-3.100 (-5, -1.5)	-3.100 (-5.1, -0.4)
s-CTX (ng/mL)			
n	256	258	514
Mean (SD)	0.493 (0.2207)	0.501 (0.2269)	0.497 (0.2236)
Median (Min, Max)	0.440 (0.12, 1.16)	0.480 (0.04, 1.52)	0.470 (0.04, 1.52)
s-P1NP (ng/mL)			
n	256	258	514
Mean (SD)	701.8487 (267.2707)	683.5556 (290.0322)	692.6666 (278.8065)
Median (Min, Max)	671.6800 (182.311, 1688.526)	630.4295 (116.485, 1945.467)	657.2740 (116.485, 1945.467)

Baseline is defined as the last available assessment prior to the first dose of study drug.
Source: Listing 16.2.6.1.1, Listing 16.2.7.2.1, Listing 16.2.7.4
[Source: t_adbase_bc.sas] 22MAR2024T2:28:21 EDC DATE: 19JAN2024T10:44:00

Table 14.1.4.2.1
Diagnosis of PMOP
(Intention-to-Treat Set)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Time since initial definitive diagnosis (month)[1]			
n	255	258	513
Mean (SD)	19.98 (35.505)	18.61 (37.353)	19.29 (36.417)
Median (Min, Max)	1.08 (0.0, 225.4)	0.67 (0.0, 250.0)	0.95 (0.0, 250.0)
Menopause duration (year)[2]			
n	256	258	514
Mean (SD)	17.6 (6.56)	17.4 (6.52)	17.5 (6.54)
Median (Min, Max)	17.0 (2, 40)	17.0 (3, 40)	17.0 (2, 40)
Are there any prior treatment for PMOP, n (%)			
Yes	55 (21.5)	59 (22.9)	114 (22.2)
No	201 (78.5)	199 (77.1)	400 (77.8)
Current clinical symptoms, n (%)[3]			
None	119 (46.5)	109 (42.2)	228 (44.4)
Pain	113 (44.1)	126 (48.8)	239 (46.5)
Spinal Deformity	5 (2.0)	6 (2.3)	11 (2.1)
Fracture	16 (6.3)	18 (7.0)	34 (6.6)
Loss of Height	11 (4.3)	11 (4.3)	22 (4.3)
Other	9 (3.5)	7 (2.7)	16 (3.1)

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
[1] Duration of Initial Definite Diagnosis(month) means the duration from the target date to the ICF date. Equal to (ICFs date - Target date + 1)/30.4375.
[2] Menopause duration (year) means the duration from the target date to the ICF date. Equal to ICFs date (year) - Target date (year).
[3] Subjects had multiple symptoms was calculated in each specific category.
Source: Listing 16.2.4.2
[Source: t_adbase_pmop.sas] 22MAR2024T2:28:27 EDC DATE: 19JAN2024T10:44:00

Table 14.1.4.3.1
Fracture History
(Intention-to-Treat Set)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Time since latest fracture (year)[1]			
n	91	92	183
Mean (SD)	7.7 (11.02)	7.7 (8.61)	7.7 (9.86)
Median (Min, Max)	5.0 (0, 53)	4.0 (0, 35)	4.0 (0, 53)
Anatomical Site of Fracture, n (%)[2]			
Hip	6 (2.3)	12 (4.7)	18 (3.5)
Ribs	7 (2.7)	6 (2.3)	13 (2.5)
Upper limb	30 (11.7)	33 (12.8)	63 (12.3)
Lower limb	23 (9.0)	26 (10.1)	49 (9.5)
Spine or Vertebrae	39 (15.2)	37 (14.3)	76 (14.8)
Clavicle	2 (0.8)	3 (1.2)	5 (1.0)
Unknown	0	1 (0.4)	1 (0.2)
Other	0	1 (0.4)	1 (0.2)
Fracture Severity, n (%)[3]			
Mild	36 (14.1)	37 (14.3)	73 (14.2)
Moderate	8 (3.1)	8 (3.1)	16 (3.1)
Severe	4 (1.6)	3 (1.2)	7 (1.4)
Unknown	37 (14.5)	44 (17.1)	81 (15.8)
Not evaluable	7 (2.7)	3 (1.2)	10 (1.9)
Fracture ongoing, n (%)[4]			
Yes	10 (3.9)	7 (2.7)	17 (3.3)
No	82 (32.0)	88 (34.1)	170 (33.1)

Table 14.1.4.3.1
Fracture History
(Intention-to-Treat Set)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
[1] Duration (year) means the duration from the target date to the reference date. Reference date is the ICF date. Equal to ICFs date(year) - Target date (year).
[2] If subjects with more than one anatomical site of fracture, then counts + 1 for fracture site respectively.
[3] If subjects with more than one anatomical site of fracture and different severity, then counts + 1 for the most serious severity.
[4] "No" means all fractures ended or no fracture is ongoing.
Source: Listing 16.2.4.5
[Source: t_admh_fh.sas] 22MAR2024T2:46:10 EDC DATE: 19JAN2024T10:44:00

Treatment period 2

Based on the extension SS, the median age of subjects in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups were 66.0 (range: 52-86) years, 67.0 (range: 51-79) years and 67.0 (range: 55-86) years. The majority of subjects were Asian (HLX14/HLX14 group vs. Prolia/HLX14 group vs. Prolia/Prolia group: 219 [99.5%] vs. 109 [99.1%] vs. 110 [100%]). The mean (SD) BMI was 23.34 (2.915) kg/m2, 23.87 (2.893) kg/m2 and 23.11 (3.090) kg/m2, respectively. The majority of subjects never smoked (217 [98.6%] vs. 108 [98.2%] vs. 107 [97.3%]) or consumed alcohol (214 [97.3%] vs. 107 [97.3%] vs. 109 [99.1%]). None of the subjects engaged in alcohol abuse. The majority of subjects had no history of medicine allergies (205 [93.2%] vs. 106 [96.4%] vs. 105 [95.5%]) and any other allergic history (216 [98.2%] vs. 108 [98.2%] vs. 107 [97.3%]). The majority of subjects did not have any family history of hip fracture (206 [93.6%] vs. 102 [92.7%] vs. 99 [90.0%]) or previously receive bisphosphonates (210 [95.5%] vs. 106 [96.4%] vs. 106 [96.4%]). Based on the extension SS, the mean (SD) BMD at the lumbar spine assessed by the central imaging for subjects in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups were 0.7350 (0.0782) g/cm2, 0.7396 (0.0808) g/cm2 and 0.7447 (0.0768) g/cm2, respectively; the mean (SD) BMD at the total hip assessed by the central imaging were 0.7110 (0.0919) g/cm2, 0.7055 (0.0886) g/cm2 and 0.7146 (0.0934) g/cm2, respectively; the mean (SD) BMD at the femoral neck assessed by the central imaging were 0.6165 (0.1026) g/cm2, 0.6196 (0.0921) g/cm2 and 0.6261 (0.1117) g/cm2, respectively; the mean (SD) T-score at the lumbar spine assessed by the central imaging were −3.216 (0.5707), −3.220 (0.5259) and −3.187 (0.5567), respectively; the mean (SD) s-CTX were 0.504 (0.2187) ng/mL, 0.513 (0.2244) ng/mL and 0.471 (0.2136) ng/mL, respectively; the mean (SD) s-P1NP were 711.1694 (259.4776) ng/mL, 732.1761 (333.1961) ng/mL and 629.7640 (239.7410) ng/mL, respectively.

Based on the extension SS, the mean (SD) time since initial definitive diagnosis of PMOP for subjects in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups were 21.36 (36.525) months, 17.80 (36.673) months and 16.24 (32.842) months, respectively. The mean (SD) menopause duration was 17.3 (6.16) years, 16.8 (6.31) years and 17.1 (5.80) years, respectively. A similar percentage of subjects in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups had prior treatment for PMOP (50 [22.7%] vs. 24 [21.8%] vs. 26 [23.6%]). For current clinical symptoms, the percentage of subjects with no clinical symptoms (98 [44.5%] vs. 49 [44.5%] vs. 40 [36.4%]) and pain (100 [45.5%] vs. 54 [49.1%] vs. 57 [51.8%]) were comparable among the three treatment groups.

Based on the extension SS, the number of subjects with a fracture history in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups were 76 (34.5%), 33 (30.0%) and 49 (44.5%), respectively. The mean (SD) time since latest fracture were 7.0 (10.75) years, 5.7 (4.78) years and 9.3 (10.19) years, respectively. The anatomical sites of fracture were as follows: spine or vertebrae (33 [15.0%] vs. 16 [14.5%] vs. 14 [12.7%]), upper limb (27 [12.3%] vs. 12 [10.9%] vs. 19 [17.3%]), lower limb (18 [8.2%] vs. 9 [8.2%] vs. 15 [13.6%]), ribs (5 [2.3%] vs. 2 [1.8%] vs. 4 [3.6%]), hip (4 [1.8%] vs. 2 [1.8%] vs. 9 [8.2%]) and clavicle (2 [0.9%] vs. 2 [1.8%] vs. 1 [0.9%]). The percentage of subjects with fracture severity of mild (30 [13.6%] vs. 12 [10.9%] vs. 22 [20.0%]), moderate (7 [3.2%] vs. 2 [1.8%] vs. 3 [2.7%]) and severe (4 [1.8%] vs. 1 [0.9%] vs. 1 [0.9%]) were similar among the three treatment groups. Nine (4.1%), 2 (1.8%) and 3 (2.7%) subjects had ongoing fracture in the three treatment groups, respectively.

Numbers analysed

All 514 subjects enrolled in the study were included in the ITT set and SS. A total of 459 subjects (HLX14 group vs. Prolia group: 225/256 vs. 234/258) were included in the PPS, and 55 subjects (31 vs. 24) were excluded from the PPS. A total of 506 subjects (252/256 vs. 254/258) were included in

the PKS, and 8 subjects (4 subjects in each group) were excluded from the PKS. A total of 471 subjects (234/256 vs. 237/258) were included in the PDS, and 43 subjects (22 vs. 21) were excluded from the PDS.

Table 16. **Analysis Population (Intention to Treat set)**

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Intention-to-Treat Set (ITT)[1], n (%)	256 (100)	258 (100)	514 (100)
Per Protocol Set (PPS)[2], n (%)	225 (87.9)	234 (90.7)	459 (89.3)
Subjectsexcluded and excluded reasons, n (%)	31 (12.1)	24 (9.3)	55 (10.7)
Subjects did not take the second dose	20 (7.8)	20 (7.8)	40 (7.8)
Subjects did not take the second dose and took prohibited drug "cervus and cucumis polypeptide for injection, dose 100 mg, daily" for 12 days before Week 26	1 (0.4)	0	1 (0.2)
Subjects did not take the second dose and took the prohibited drug "jiegu qili jiaonang" for 16 days before week 52	0	1 (0.4)	1 (0.2)
Subjects did not take the second dose and took the prohibited drug "menatetrenone soft capsules" for about 20 days before Week 52	1 (0.4)	0	1 (0.2)
Subjects met the exclusion criteria 1: subjects with elevated parathyroid hormone	1 (0.4)	0	1 (0.2)
Subjects met the exclusion criteria 2: subjects with hyperthyroidism	1 (0.4)	0	1 (0.2)
Subjects took the prohibited drug "gu sui bu, dose 15 g, daily" for 10 days before Week 26	1 (0.4)	0	1 (0.2)
Subjects took the prohibited drug "jin tian ge capsule 1.2 g, po, tid." over 25 days before Week 52	1 (0.4)	0	1 (0.2)
Subjects took the prohibited drug "methylprednisolone sodium succinate for injection" 5 days before Week 52	0	1 (0.4)	1 (0.2)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects took the prohibited drug "methylprednisolone sodium succinate for injection 40 mg ivgtt" for 4 days before Week 52	1 (0.4)	0	1 (0.2)
Subjects took the prohibited drug "xin tong kou fu ye (traditional Chinese medicine)" for 6 days before Week 26	1 (0.4)	0	1 (0.2)
Subjects took the prohibited drug "yangxinshipian" over one month before Week 26	1 (0.4)	0	1 (0.2)
Subjects took the prohibited drug "gushukang capsule, 1.28 g twice daily" for 20 days before Week 52	0	1 (0.4)	1 (0.2)
Subjects took the prohibited drug "prednisone acetate tablets, 10mg, BID" for 4 days before Week 26	0	1 (0.4)	1 (0.2)
Subjects took the prohibited drug "with prednisone acetate tablets (20 mg.TID PO) " for 6 days before Week 26	1 (0.4)	0	1 (0.2)
Subjects took the second dose 3 months earlier than scheduled Week 26.	1 (0.4)	0	1 (0.2)
Safety Set (SS)[3], n (%)	256 (100)	258 (100)	514 (100)
Pharmacokinetic Set (PKS)[4], n (%)	252 (98.4)	254 (98.4)	506 (98.4)
Subjects excluded and excluded reasons, n (%)	4 (1.6)	4 (1.6)	8 (1.6)
No post-dose serum concentration at a scheduled sampling time point was available.	4 (1.6)	4 (1.6)	8 (1.6)
Pharmacodynamic Set (PDS)[5], n (%)	234 (91.4)	237 (91.9)	471 (91.6)
Subjects excluded and excluded reasons, n (%)	22 (8.6)	21 (8.1)	43 (8.4)
The subject's s-CTX $AUEC_{0\text{-}26W}$ can not be calculated due to missing blood sample collection on Day 183.	21 (8.2)	21 (8.1)	42 (8.2)
The subject's s-CTX $AUEC_{0\text{-}26W}$ cannot be calculated due to the early administration of the second dose long before Day 183.	1 (0.4)	0	1 (0.2)

N: The number of subjects in the ITT set; n: The number of subjects in specific category; %: (n/N*100)
po: Peros; tid: Ter in die; ivgtt: Intravenously guttae.
[1] Intention-To-Treat (ITT) set: Defined as all postmenopausal women with osteoporosis at high risk of fracture who were randomized in this study.
[2] Per Protocol Set (PPS): The per protocol set was a subset of ITT, and the PPS was consisted of all subjects randomized without major protocol deviations that significantly affected the primary efficacy assessment.
[3] Safety set (SS): Defined as all subjects who received at least one dose of the study drug.
[4] Pharmacokinetic set (PKS): Defined as all randomized subjects who received at least one dose of HLX14 or Prolia® and had at least one post-dose serum concentration at a scheduled sampling time point, without protocol deviations that could significantly affect the pharmacokinetic profile of the study drug.
[5] Pharmacodynamic set (PDS): All subjects who were randomized to receive at least one dose of study drug and had at least one post-administration PD concentration at the planned PD sample collection time point without significant protocol violation or deviation from the evaluation of the s-CTX $AUEC_{0\text{-}26W}$.
Data source: Table 14.1.3.1.

Outcomes and estimation

Efficacy results

Primary efficacy analyses

Based on the ITT set, the mean (SD) percent change from baseline to week 52 in BMD at the lumbar spine assessed by central imaging for subjects in the HLX14 and Prolia groups were 6.10% (3.928%) and 5.96% (3.894%), respectively. The LS mean difference adjusted for baseline BMD values and stratification factor BMI (< 25, 25–30, > 30) using ANCOVA model between the HLX14 group and Prolia group was 0.21% (95% CI: -0.51%, 0.94%). The 95% CI for the difference fell within the pre-

specified equivalence margins (-1.45%, 1.45%), confirming the similarity in clinical efficacy between HLX14 and Prolia.

Percent change from baseline in BMD at the lumbar spine to Week 52 (D365)

Table 11-3 Descriptive Summary of Percent Changes from Baseline to Week 52 in BMD at Lumbar Spine Assessed by Central Imaging - Hypothesis Strategy (Intention-to-Treat Set)

Time Point	Statistic	HLX14 (N=256)	Prolia® (N=258)
Baseline	n	256	258
	Mean (SD)	0.7365 (0.0793)	0.7394 (0.0793)
	Median	0.7345	0.7325
	Min, Max	0.485, 0.907	0.542, 0.916
Week 52	n	217	226
	Mean (SD)	0.7794 (0.0852)	0.7828 (0.0852)
	Median	0.7810	0.7840
	Min, Max	0.521, 0.998	0.586, 1.01
Changes from baseline - Week 52	n	217	226
	Mean (SD)	0.0445 (0.0287)	0.0435 (0.0283)
	Median	0.0450	0.0430
	Min, Max	-0.039, 0.124	-0.042, 0.14
Percent Changes from Baseline - Week 52(%)	n	217	226
	Mean (SD)	6.10 (3.928)	5.96 (3.894)
	Median	6.17	5.84
	Min, Max	-6.1, 15.0	-4.8, 19.7

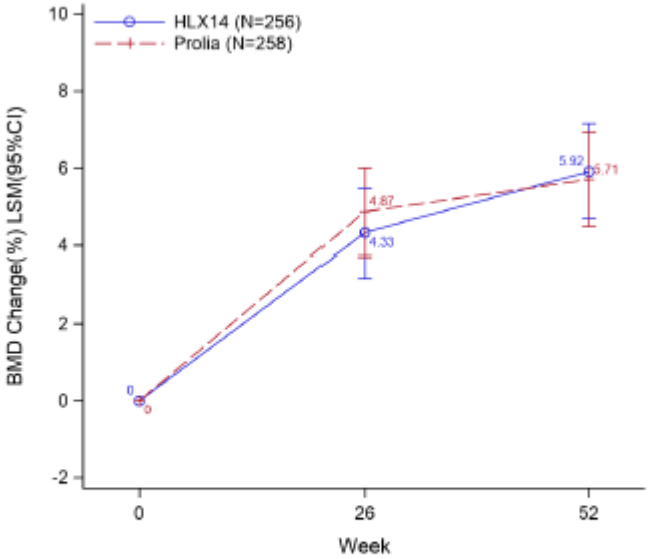
Hypothesis strategy was mainly applied for intercurrent events (ICEs) such as premature treatment discontinuation before Week 26, use of prohibited drugs, and so on. This table summarizes the data before imputing missing data.
Data source: Table 14.2.1.1.9.

Table 11-4 ANCOVA Model for Percent Changes from Baseline to Week 52 in BMD at Lumbar Spine Assessed by Central Imaging (Intention-To-Treat Set)

Time Point	Statistic	HLX14 (N=256)	Prolia® (N=258)
Percent Changes from Baseline - Week 52 (%)	LS Mean (SE)[1]	5.92 (0.633)	5.71 (0.625)
	LS Mean 95% CI[1]	4.68, 7.16	4.48, 6.93
	LS Mean Difference (vs. Prolia) (95% CI)[1]	0.21 (-0.51, 0.94)	
	P-value	0.560	
	LS Mean 90% CI[1]	4.88, 6.96	4.68, 6.74
	LS Mean Difference (vs. Prolia) (90% CI)[1]	0.21 (-0.39, 0.82)	
	P-value	0.560	

Hypothesis strategy was mainly applied for intercurrent events (ICEs) such as premature treatment discontinuation before Week 26, use of prohibited drugs, and so on, for subjects with treatment discontinuation before Week 26 due to adverse event or lack of efficacy, or with new fractures (treatment related), missing data was imputed using worst-observation-carried forward (WOCF). Others were multiple imputed based on MAR.
[1] Analysis of Covariance (ANCOVA), which was with treatment group, stratification factors BMI (< 25, 25 - 30, > 30) as factors, and baseline BMD values as covariates.
Data source: Table 14.2.1.1.1.

Figure 11-1 Percent Change from Baseline to Week 52 in BMD at Lumbar Spine Over Time Assessed by Central Imaging - Primary ANCOVA Analysis (Intention-To-Treat Set)



Hypothesis strategy was mainly applied for intercurrent events (ICEs) such as premature treatment discontinuation before Week 26, use of prohibited drugs, and so on, for subjects with treatment discontinuation before Week 26 due to adverse event or lack of efficacy, or with new fractures (treatment related), missing data was imputed using worst-observation-carried forward (WOCF). Others were multiple imputed based on MAR.
LS Mean (95% CI) were from analysis of covariance (ANCOVA), which was with treatment group, stratification factors BMI (< 25, 25 - 30, > 30) as factors, and baseline BMD values as covariates.

Supplementary analysis based on the PPS

Based on the PPS, at Week 52, the LS mean (SE) percent change from baseline in BMD at the lumbar spine assessed by central imaging for subjects in the HLX14 and Prolia groups were 5.89% (0.628%) and 5.79% (0.619%), respectively. Based on the ANCOVA model, the LS mean difference between the HLX14 group and Prolia group was 0.10% (95% CI: -0.62%, 0.83%). The analysis results based on the PPS were consistent with the primary analysis conclusion based on the ITT set.

Table 11-10 ANCOVA Model for Percent Changes from Baseline to Week 52 in BMD at Lumbar Spine Assessed by Central Imaging (Per Protocol Set)

Time Point	Statistic	HLX14 (N=225)	Prolia® (N=234)
Percent Changes from Baseline - Week 52 (%)	LS Mean (SE)[1]	5.89 (0.628)	5.79 (0.619)
	LS Mean 95% CI[1]	4.66, 7.12	4.57, 7.00
	LS Mean Difference (vs. Prolia) (95% CI)[1]	0.10 (-0.62, 0.83)	
	P-value	0.777	
	LS Mean 90% CI[1]	4.86, 6.92	4.77, 6.81
	LS Mean Difference (vs. Prolia) (90% CI)[1]	0.10 (-0.50, 0.71)	
	P-value	0.777	

Hypothesis strategy was mainly applied for intercurrent events (ICEs) such as premature treatment discontinuation before Week 26, use of prohibited drugs, and so on, for subjects with treatment discontinuation before Week 26 due to adverse event or lack of efficacy, or with new fractures (treatment related), missing data was imputed using worst-observation-carried forward (WOCF). Others were multiple imputed based on MAR.
[1] Analysis of Covariance (ANCOVA), which was with treatment group, stratification factors BMI (< 25, 25 - 30, > 30) as factors, and baseline BMD values as covariates.
Data source: Table 14.2.1.1.5.

Sensitivity analysis 1: Mixed-effect model for repeated measures (MMRM)

Table 11-5 MMRM for Percent Changes from Baseline to Week 52 in BMD at Lumbar Spine Assessed by Central Imaging (Intention-to-Treat Set)

Time Point	Statistic	HLX14 (N=256)	Prolia® (N=258)
Percent Changes from Baseline - Week 52 (%)	LS Mean (SE)[1]	6.10 (0.263)	5.88 (0.257)
	LS Mean 95% CI[1]	5.59, 6.62	5.37, 6.38
	LS Mean Difference (vs. Prolia) (95% CI)[1]	0.23 (-0.49, 0.95)	
	P-value	0.534	
	LS Mean 90% CI[1]	5.67, 6.54	5.45, 6.30
	LS Mean Difference (vs. Prolia) (90% CI)[1]	0.23 (-0.38, 0.84)	
	P-value	0.534	

Hypothesis strategy was mainly applied for intercurrent events (ICEs) such as premature treatment discontinuation before Week 26, use of prohibited drugs, and so on, for subjects with treatment discontinuation before Week 26 due to adverse event or lack of efficacy, or with new fractures (treatment related), missing data was imputed using worst-observation-carried forward (WOCF).
[1] Mixed model for repeated measures (MMRM), which was with treatment group, stratification factor BMI (< 25, 25 - 30, > 30), visit and treatment by visit interaction as factors, and the respective baseline BMD values as covariates, an unstructured covariance matrix was used to model the covariance structure.
Data source: Table 14.2.1.1.2.

Sensitivity analysis 2: Tipping point analysis

Based on the ITT set, the tipping point analysis was performed to explore the sensitivity of results to violations in assumptions about the missing data. The conclusion (95% CI for the difference fell within the pre-specified equivalence margins) would be reversed only if the penalty level is exceedingly large (negative penalty: shift for Prolia decreases by 6% or more or shift for HLX14 decreases by 8% or more; positive penalty: shift for Prolia increases by 9% or more or shift for HLX14 increases by 5% or more), which seems implausible. Therefore, the results of the tipping point method further supported the finding of the primary analysis result.

Table 11-6 ANCOVA Model for Percent Changes from Baseline to Week 52 in BMD at Lumbar Spine Assessed by Central Imaging Using Tipping Point Method (Intention-To-Treat Set)

Negative penalty

		Shift for the BMD at week 52 in Prolia®								
		0	-1%	-2%	-3%	-4%	-5%	-6%	-7%	-8%
Shift for the BMD at Week 52 in HLX14	0	0.16 (-0.56, 0.88)	0.25 (-0.47, 0.98)	0.35 (-0.38, 1.07)	0.44 (-0.29, 1.17)	0.53 (-0.20, 1.27)	0.63 (-0.12, 1.37)	0.72 (-0.03, 1.48)	0.81 (0.05, 1.58)	0.91 (0.13, 1.69)
	-1%	0.05 (-0.67, 0.77)	0.15 (-0.58, 0.87)	0.24 (-0.49, 0.96)	0.33 (-0.40, 1.06)	0.42 (-0.31, 1.16)	0.52 (-0.23, 1.26)	0.61 (-0.14, 1.37)	0.70 (-0.06, 1.47)	0.80 (0.02, 1.58)
	-2%	-0.06 (-0.78, 0.67)	0.04 (-0.69, 0.76)	0.13 (-0.60, 0.86)	0.22 (-0.51, 0.96)	0.32 (-0.42, 1.06)	0.41 (-0.34, 1.16)	0.50 (-0.26, 1.26)	0.60 (-0.17, 1.36)	0.69 (-0.09, 1.47)
	-3%	-0.17 (-0.89, 0.56)	-0.07 (-0.80, 0.66)	0.02 (-0.71, 0.75)	0.11 (-0.62, 0.85)	0.21 (-0.54, 0.95)	0.30 (-0.45, 1.05)	0.39 (-0.37, 1.15)	0.49 (-0.29, 1.26)	0.58 (-0.21, 1.36)
	-4%	-0.28 (-1.01, 0.46)	-0.18 (-0.92, 0.55)	-0.09 (-0.83, 0.65)	0.00 (-0.74, 0.75)	0.10 (-0.65, 0.85)	0.19 (-0.57, 0.95)	0.28 (-0.48, 1.05)	0.38 (-0.40, 1.16)	0.47 (-0.32, 1.26)
	-5%	-0.39 (-1.13, 0.36)	-0.29 (-1.04, 0.45)	-0.20 (-0.95, 0.55)	-0.11 (-0.86, 0.65)	-0.01 (-0.77, 0.75)	0.08 (-0.69, 0.85)	0.17 (-0.60, 0.95)	0.27 (-0.52, 1.05)	0.36 (-0.44, 1.16)
	-6%	-0.49 (-1.25, 0.26)	-0.40 (-1.16, 0.35)	-0.31 (-1.07, 0.45)	-0.21 (-0.98, 0.55)	-0.12 (-0.89, 0.65)	-0.03 (-0.80, 0.75)	0.06 (-0.72, 0.85)	0.16 (-0.64, 0.95)	0.25 (-0.56, 1.06)
	-7%	-0.60 (-1.37, 0.16)	-0.51 (-1.28, 0.26)	-0.42 (-1.19, 0.35)	-0.32 (-1.10, 0.45)	-0.23 (-1.01, 0.55)	-0.14 (-0.93, 0.65)	-0.04 (-0.84, 0.75)	0.05 (-0.76, 0.86)	0.14 (-0.68, 0.96)
	-8%	-0.71 (-1.49, 0.07)	-0.62 (-1.40, 0.16)	-0.53 (-1.31, 0.26)	-0.43 (-1.22, 0.35)	-0.34 (-1.13, 0.45)	-0.25 (-1.05, 0.55)	-0.15 (-0.96, 0.66)	-0.06 (-0.88, 0.76)	0.03 (-0.80, 0.87)

Positive penalty

		Shift for the BMD at week 52 in Prolia®									
		0	1%	2%	3%	4%	5%	6%	7%	8%	9%
Shift for the BMD at week 52 in HLX 14	0	0.16 (-0.56, 0.88)	0.07 (-0.65, 0.79)	-0.02 (-0.75, 0.70)	-0.12 (-0.85, 0.61)	-0.21 (-0.94, 0.52)	-0.30 (-1.05, 0.44)	-0.40 (-1.15, 0.35)	-0.49 (-1.25, 0.27)	-0.58 (-1.36, 0.19)	-0.68 (-1.46, 0.11)
	1%	0.27 (-0.45, 0.99)	0.18 (-0.55, 0.90)	0.08 (-0.64, 0.81)	-0.01 (-0.74, 0.72)	-0.10 (-0.84, 0.63)	-0.20 (-0.94, 0.55)	-0.29 (-1.04, 0.46)	-0.38 (-1.14, 0.38)	-0.47 (-1.25, 0.30)	-0.57 (-1.35, 0.22)
	2%	0.38 (-0.35, 1.11)	0.29 (-0.44, 1.01)	0.19 (-0.54, 0.92)	0.10 (-0.63, 0.83)	0.01 (-0.73, 0.75)	-0.09 (-0.83, 0.66)	-0.18 (-0.93, 0.58)	-0.27 (-1.04, 0.49)	-0.37 (-1.14, 0.41)	-0.46 (-1.25, 0.33)
	3%	0.49 (-0.24, 1.22)	0.40 (-0.34, 1.13)	0.30 (-0.43, 1.04)	0.21 (-0.53, 0.95)	0.12 (-0.63, 0.86)	0.02 (-0.73, 0.77)	-0.07 (-0.83, 0.69)	-0.16 (-0.93, 0.61)	-0.26 (-1.04, 0.53)	-0.35 (-1.14, 0.45)
	4%	0.60 (-0.14, 1.34)	0.51 (-0.23, 1.25)	0.41 (-0.33, 1.15)	0.32 (-0.43, 1.06)	0.23 (-0.53, 0.98)	0.13 (-0.63, 0.89)	0.04 (-0.73, 0.81)	-0.05 (-0.83, 0.72)	-0.15 (-0.94, 0.64)	-0.24 (-1.04, 0.56)
	5%	0.71 (-0.04, 1.46)	0.61 (-0.13, 1.36)	0.52 (-0.23, 1.27)	0.43 (-0.33, 1.18)	0.34 (-0.43, 1.10)	0.24 (-0.53, 1.01)	0.15 (-0.63, 0.92)	0.06 (-0.73, 0.84)	-0.04 (-0.84, 0.76)	-0.13 (-0.94, 0.68)
	6%	0.82 (0.06, 1.58)	0.72 (-0.04, 1.48)	0.63 (-0.13, 1.39)	0.54 (-0.23, 1.30)	0.44 (-0.33, 1.22)	0.35 (-0.43, 1.13)	0.26 (-0.53, 1.04)	0.16 (-0.63, 0.96)	0.07 (-0.74, 0.88)	-0.02 (-0.84, 0.80)
	7%	0.93 (0.15, 1.70)	0.83 (0.06, 1.61)	0.74 (-0.04, 1.52)	0.65 (-0.13, 1.43)	0.55 (-0.23, 1.34)	0.46 (-0.33, 1.25)	0.37 (-0.43, 1.17)	0.27 (-0.54, 1.08)	0.18 (-0.64, 1.00)	0.09 (-0.75, 0.92)
	8%	1.04 (0.25, 1.82)	0.94 (0.15, 1.73)	0.85 (0.06, 1.64)	0.76 (-0.04, 1.55)	0.66 (-0.14, 1.46)	0.57 (-0.24, 1.38)	0.48 (-0.34, 1.29)	0.38 (-0.44, 1.21)	0.29 (-0.54, 1.12)	0.20 (-0.65, 1.04)
	9%	1.15 (0.34, 1.95)	1.05 (0.25, 1.86)	0.96 (0.15, 1.76)	0.87 (0.06, 1.68)	0.77 (-0.04, 1.59)	0.68 (-0.14, 1.50)	0.59 (-0.24, 1.42)	0.49 (-0.35, 1.33)	0.40 (-0.45, 1.25)	0.31 (-0.56, 1.17)

White cells represented the 95% CIs of LS mean difference falling within the pre-specified equivalence margins (non-reversed results), gray cells represented the 95% CIs of LS mean difference exceed the pre-specified equivalence margins (reversed results).
Hypothesis strategy was mainly applied for intercurrent events (ICEs) such as premature treatment discontinuation before Week 26, use of prohibited drugs, and so on. Missing Week 52 data was multiple imputed based on MAR, and for each arm a penalty was added to the imputed values at Week 52 where treatment related ICEs (premature treatment discontinuation due to any reason, use of prohibited drugs and treatment related fractures) happened. The approach was to gradually increase this penalty until the BMD conclusion from the primary analysis was changed.
[1] Analysis of Covariance (ANCOVA), which was with treatment group, stratification factors BMI (< 25, 25 - 30, > 30) as factors, and baseline BMD values as covariates.
Data source: Table 14.2.1.1.3.

Sensitivity analysis 3: Treatment policy

Based on the ITT set, the mean (SD) percent change from baseline to week 52 in BMD at the lumbar spine assessed by central imaging for subjects in the HLX14 and Prolia groups were 5.93% (4.021%) and 5.87% (4.001%), respectively. The LS mean difference adjusted for baseline BMD values and stratification factor BMI (< 25, 25–30, > 30) using MMRM model between the HLX14 group and Prolia group was 0.08% (95% CI: -0.64%, 0.79%), the 95% CI for the difference fell within the pre-specified equivalence margins (-1.45%, 1.45%). The results were consistent with the primary analysis conclusion.

Table 11-7 MMRM for Percent Changes from Baseline to Week 52 in BMD at Lumbar Spine Assessed by Central Imaging - Treatment Policy (Intention-To-Treat Set)

Time Point	Statistic	HLX14 (N=256)	Prolia® (N=258)
Percent Changes from Baseline - Week 52 (%)	LS Mean (SE)[1]	5.94 (0.258)	5.87 (0.255)
	LS Mean 95% CI[1]	5.44, 6.45	5.37, 6.37
	LS Mean Difference (vs. Prolia) (95% CI)[1]	0.08 (-0.64, 0.79)	
	P-value	0.835	
	LS Mean 90% CI[1]	5.52, 6.37	5.45, 6.29
	LS Mean Difference (vs. Prolia) (90% CI)[1]	0.08 (-0.52, 0.67)	
	P-value	0.835	

Treatment Policy was applied for intercurrent events (ICEs) and Week 26, Week 52 data collected after ICEs happened were used.
[1] Mixed model for repeated measures (MMRM), which was with treatment group, stratification factor BMI (< 25, 25 - 30, > 30), visit and treatment by visit interaction as factors, and the respective baseline BMD values as covariates, an unstructured covariance matrix was used to model the covariance structure.
Data source: Table 14.2.1.1.4.

Sensitivity analysis 4: Using BMD measurement from the investigator

Based on the ITT set, the mean (SD) percent change from baseline to week 52 in BMD at the lumbar spine assessed by the Investigator for subjects in the HLX14 and Prolia groups were 5.77% (4.342%)

and 5.95% (4.723%), respectively. The LS mean difference adjusted for baseline BMD values and stratification factor BMI (< 25, 25–30, > 30) using MMRM model between the HLX14 group and Prolia group was -0.10% (95% CI: -0.94%, 0.73%), the 95% CI for the difference fell within the pre-specified equivalence margins (-1.45%, 1.45%). The results were consistent with the primary analysis conclusion.

Table 11-8 MMRM for Percent Changes from Baseline to Week 52 in BMD at Lumbar Spine Assessed by the Investigator (Intention-To-Treat Set)

Time Point	Statistic	HLX14 (N=256)	Prolia® (N=258)
Percent Changes from Baseline - Week 52 (%)	LS Mean (SE)[1]	5.76 (0.304)	5.87 (0.297)
	LS Mean 95% CI[1]	5.16, 6.36	5.28, 6.45
	LS Mean Difference (vs. Prolia) (95% CI)[1]	-0.10 (-0.94, 0.73)	
	P-value	0.805	

Hypothesis strategy was mainly applied for intercurrent events (ICEs) such as premature treatment discontinuation before Week 26, use of prohibited drugs, and so on, for subjects with treatment discontinuation before Week 26 due to adverse event or lack of efficacy, or with new fractures (treatment related), missing data was imputed using worst-observation-carried forward (WOCF).
[1] Mixed model for repeated measures (MMRM), which was with treatment group, stratification factor BMI (< 25, 25 - 30, > 30), visit and treatment by visit interaction as factors, and the respective baseline BMD values as covariates, an unstructured covariance matrix was used to model the covariance structure.
Data source: Table 14.2.1.2.1.

Sensitivity analysis 5: Add age (< 65 years, ≥ 65 years) and prior bisphosphonate use (yes/ no) in the multiple imputation

Based on the ITT set, at Week 52, the LS mean (SE) percent change from baseline in BMD at the lumbar spine assessed by central imaging for subjects in the HLX14 and Prolia groups were 5.41% (0.808%) and 5.20% (0.801%), respectively. Based on the ANCOVA model, the LS mean difference between the HLX14 group and Prolia group was 0.21% (95% CI: -0.51%, 0.92%), the 95% CI for the difference fell within the pre-specified equivalence margins (-1.45%, 1.45%). The results were consistent with the primary analysis conclusion.

Table 11-9 ANCOVA Model for Percent Changes from Baseline to Week 52 in BMD at Lumbar Spine Assessed by Central Imaging - Covariate Adjusted (Intention-to-Treat Set)

Time Point	Statistic	HLX14 (N=256)	Prolia® (N=258)
Percent Changes from Baseline - Week 52 (%)	LS Mean (SE)[1]	5.41 (0.808)	5.20 (0.801)
	LS Mean 95% CI[1]	3.82, 6.99	3.63, 6.77
	LS Mean Difference (vs. Prolia) (95% CI)[1]	0.21 (-0.51, 0.92)	
	P-value	0.570	
	LS Mean 90% CI[1]	4.08, 6.74	3.88, 6.52
	LS Mean Difference (vs. Prolia) (90% CI)[1]	0.21 (-0.39, 0.81)	
	P-value	0.570	

Hypothesis strategy was mainly applied for intercurrent events (ICEs) such as premature treatment discontinuation before Week 26, use of prohibited drugs, and so on, for subjects with treatment discontinuation before Week 26 due to adverse event or lack of efficacy, or with new fractures (treatment related), missing data was imputed using worst-observation-carried forward (WOCF). Others were multiple imputed based on MAR.
[1] Analysis of Covariance (ANCOVA), which was with treatment group, stratification factors BMI (< 25, 25 - 30, > 30), age (< 65 years, ≥ 65 years) and prior bisphosphonate use (yes/no) as factors, and baseline BMD values as covariates.
Data source: Table 14.2.1.1.6.

Secondary efficacy analyses

Fracture rate from baseline to Week 52, 78

Based on the ITT set, with the application of hypothesis strategy for handling ICEs, from baseline to Week 52, 10 (3.9%) subjects experienced new fractures in both the HLX14 and Prolia groups. The adjusted risk difference between the HLX14 group and the Prolia group was 0.0 (95% CI: −3.3%, 3.4%). The relative risk between the HLX14 group and the Prolia group was 1.00 (95% CI: 0.97, 1.04).

Based on the extension efficacy set, with the application of hypothesis strategy for handling ICEs, from baseline to Week 78, 13 (6.0%), 8 (7.6%) and 6 (5.6%) subjects experienced new fractures in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups, respectively. The adjusted risk differences between the HLX14/HLX14 and Prolia/Prolia groups, and between the Prolia/HLX14 and Prolia/Prolia groups were 0.4% (95% CI: −5.0%, 5.8%) and 2.5% (95% CI: −4.2%, 9.2%), respectively; the relative risks were 1.00 (95% CI: 0.95, 1.06) and 1.03 (95% CI: 0.96, 1.10), respectively.

In summary, with the application of hypothesis strategy for handling ICEs, the rate of new fractures from baseline to Week 52 was similar between the HLX14 and Prolia groups; the rate of new fractures from baseline to Week 78 in fracture rate was similar among the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups.

Table 11-11 Summary of Fracture Rate from Baseline to Week 52 by Treatment (Intention-to-Treat Set)

Time Point	Statistic	HLX14 (N=256)	Prolia® (N=258)
Baseline to Week 52	Subjects with new fracture n (%) [95% CI][1]	10 (3.9) [1.9, 7.1]	10 (3.9) [1.9, 7.0]
	Absolute risk difference (95% CI) (vs. Prolia)[2]	0.0 (-3.3, 3.4)	
	P-value	0.986	
	Adjusted risk difference (95% CI) (vs. Prolia)[3]	0.0 (-3.3, 3.4)	
	P-value	0.994	
	Relative risk (95% CI) (vs. Prolia)[3]	1.00 (0.97, 1.04)	
	P-value	0.994	

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
[1] Exact two-sided 95% CI by Clopper and Pearson was presented.
[2] Absolute risk difference (95% CI) based on crude estimates with 95% CI using the normal approximation method was displayed as well. In the event that the number of subjects with new fracture was too small (ie. ≤5), the exact method (eg. Fisher's Exact test and exact unconditional confidence limits) was performed instead.
[3] Adjusted risk difference (95% CI), relative risk (95% CI) and *P*-value were from Cochran Mantel-Haenszel model, which was adjusted for stratification factors BMI (< 25, 25 - 30, > 30).
Data source: Table 14.2.2.1.

All sensitivity analyses (1. Based on the ITT set, hypothesis strategy was applied, fracture rate was analyzed without considering stratification factors, 2. Based on the ITT set, hypothesis strategy was applied, and for ICE of treatment discontinuation due to efficacy or AE, used "fracture occurs" imputation, 3. All ICEs applied treatment policy) led to similar results as the primary analysis.

Percent change in BMD at the lumbar spine from baseline to Week 26 (D183)

Based on the ITT set, with the application of hypothesis strategy for handling ICEs, the LS mean (SE) percent change from baseline to Week 26 in BMD at the lumbar spine assessed by the central imaging using MMRM for subjects in the HLX14 and Prolia groups was 3.90% (0.242%) and 4.41% (0.239%), respectively; the LS mean difference between the HLX14 group and the Prolia group was −0.51% (95% CI: −1.18%, 0.16%).

Based on the extension efficacy set, with the application of hypothesis strategy for handling ICEs, the LS mean (SE) percent change from baseline to Week 78 in BMD at the lumbar spine assessed by the central imaging using MMRM for subjects in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups were 6.99% (0.302%), 7.09% (0.435%) and 6.36% (0.427%), respectively; the LS mean differences between the HLX14/HLX14 group and the Prolia/Prolia group, and between the Prolia/HLX14 group and the Prolia/Prolia group were 0.63% (95% CI: −0.40%, 1.66%) and 0.73% (95% CI: −0.47%, 1.93%), respectively.

In summary, with the application of hypothesis strategy for handling ICEs, percent change from baseline to Week 26 in BMD at the lumbar spine assessed by the central imaging using MMRM was similar between the HLX14 and Prolia groups; percent change from baseline to Week 78 in BMD at the lumbar spine assessed by the central imaging using MMRM was similar among the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups.

Table 11-12 MMRM for Percent Change from Baseline to Week 26 in BMD at Lumbar Spine Assessed by Central Imaging (Intention-to-Treat Set)

Time Point	Statistic	HLX14 (N=256)	Prolia® (N=258)
Percent Changes from Baseline - Week 26 (%)	LS Mean (SE)[1]	3.90 (0.242)	4.45 (0.238)
	LS Mean 95% CI[1]	3.43, 4.38	3.98, 4.92
	LS Mean Difference (vs. Prolia) (95% CI)[1]	-0.55 (-1.22, 0.12)	
	P-value	0.107	
	LS Mean 90% CI[1]	3.50, 4.30	4.06, 4.84
	LS Mean Difference (vs. Prolia) (90% CI)[1]	-0.55 (-1.11, 0.01)	
	P-value	0.107	

Hypothesis strategy was mainly applied for intercurrent events (ICEs) such as premature treatment discontinuation before Week 26, use of prohibited drugs, and so on, for subjects with treatment discontinuation before Week 26 due to adverse event or lack of efficacy, or with new fractures (treatment related), missing data was imputed using worst-observation-carried forward (WOCF).
[1] Mixed model for repeated measures (MMRM), which was with treatment group, stratification factor BMI (< 25, 25 - 30, > 30), visit and treatment by visit interaction as factors, and the respective baseline BMD values as covariates, an unstructured covariance matrix was used to model the covariance structure.
Data source: Table 14.2.1.1.2.

All sensitivity analyses for the secondary endpoint Percent change in BMD at the lumbar spine from baseline to Week 26 are included in the tables of the primary endpoint.

Percent Changes in BMD at the Total Hip from Baseline to Week 26, Week 52 and Week 78 (Assessed by the Investigator)

Based on the ITT set, with the application of hypothesis strategy for handling ICEs, the mean (SD) percent changes from baseline to Week 26 in BMD at the total hip assessed by the Investigator for subjects in the HLX14 and Prolia groups were 2.32% (3.680%) and 1.98% (3.135%), respectively. Based on the MMRM, the LS mean (SE) percent changes from baseline to Week 26 in BMD at the total hip assessed by the Investigator for subjects in the HLX14 and the Prolia groups were 2.32% (0.222%) and 1.96% (0.220%), respectively; the LS mean difference between the HLX14 group and the Prolia group was 0.36% (95% CI: −0.26%, 0.97%).

Based on the ITT set, with the application of hypothesis strategy for handling ICEs, the mean (SD) percent changes from baseline to Week 52 in BMD at the total hip assessed by the Investigator for subjects in the HLX14 and Prolia groups were 3.22% (4.114%) and 2.50% (3.896%), respectively. Based on the MMRM, the LS mean (SE) percent changes from baseline to Week 52 in BMD at the total hip assessed by the Investigator for subjects in the HLX14 and Prolia groups were 3.21% (0.264%)

and 2.43% (0.260%), respectively; the LS mean difference between the HLX14 group and the Prolia group was 0.77% (95% CI: 0.05%, 1.50%).

Based on the extension efficacy set, with the application of hypothesis strategy for handling ICEs, the mean (SD) percent changes from baseline to Week 78 in BMD at the total hip assessed by the Investigator for subjects in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups were 3.82% (4.159%), 4.05% (3.647%) and 2.49% (3.803%), respectively. Based on the MMRM, the LS mean (SE) percent changes from baseline to Week 78 in BMD at the total hip assessed by the Investigator for subjects in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups were 3.82% (0.262%), 3.87% (0.379%) and 2.59% (0.370%), respectively; the LS mean differences between the HLX14/HLX14 group and the Prolia/Prolia group, and between the Prolia/HLX14 group and the Prolia/Prolia group were 1.23% (95% CI: 0.34%, 2.12%) and 1.28% (95% CI: 0.23%, 2.32%), respectively.

In summary, with the application of hypothesis strategy for handling ICEs, percent changes from baseline to Week 26 or Week 52 in BMD at the total hip assessed by the Investigator were similar between the HLX14 and Prolia groups; percent change from baseline to Week 78 in BMD at the total hip assessed by the Investigator was similar among the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups.

Table 11-13 MMRM for Percent Changes from Baseline to Week 52 in BMD at Total Hip Assessed by Central Imaging (Intention-to-Treat Set)

Time Point	Statistic	HLX14 (N=256)	Prolia® (N=258)
Percent Changes from Baseline - Week 26 (%)	LS Mean (SE)[1]	2.47 (0.174)	1.83 (0.172)
	LS Mean 95% CI[1]	2.12, 2.81	1.49, 2.17
	LS Mean Difference (vs. Prolia) (95% CI)[1]	0.63 (0.15, 1.12)	
	P-value	0.010	
Percent Changes from Baseline - Week 52 (%)	LS Mean (SE)[1]	3.43 (0.199)	2.54 (0.195)
	LS Mean 95% CI[1]	3.04, 3.82	2.15, 2.92
	LS Mean Difference (vs. Prolia) (95% CI)[1]	0.89 (0.35, 1.44)	
	P-value	0.001	

Hypothesis strategy was mainly applied for intercurrent events (ICEs) such as premature treatment discontinuation before Week 26, use of prohibited drugs, and so on.
[1] Mixed model for repeated measures (MMRM), which was with treatment group, stratification factor BMI (< 25, 25 - 30, > 30), visit and treatment by visit interaction as factors, and the respective baseline BMD values as covariates, an unstructured covariance matrix was used to model the covariance structure.
Data source: Table 14.2.3.1.1.

Percent Changes in BMD at the Femoral Neck from Baseline to Week 26, Week 52 and Week 78 (Assessed by the Investigator)

Based on the ITT set, with the application of hypothesis strategy for handling ICEs, the mean (SD) percent changes from baseline to Week 26 in BMD at the femoral neck assessed by the Investigator for subjects in the HLX14 and Prolia groups were 2.37% (4.492%) and 1.82% (3.942%), respectively. Based on the MMRM, the LS mean (SE) percent changes from baseline to Week 26 in BMD at the femoral neck assessed by the Investigator for subjects in the HLX14 and Prolia groups were 2.34% (0.273%) and 1.83% (0.270%), respectively; the LS mean difference between the HLX14 group and Prolia group was 0.51% (95% CI: −0.25%, 1.26%).

Based on the ITT set, with the application of hypothesis strategy for handling ICEs, the mean (SD) percent changes from baseline to Week 52 in BMD at the femoral neck assessed by the Investigator for

subjects in the HLX14 and Prolia groups were 2.80% (5.062%) and 2.19% (4.781%), respectively. Based on the MMRM, the LS mean (SE) percent changes from baseline to Week 52 in BMD at the femoral neck assessed by the Investigator for subjects in the HLX14 and Prolia groups were 2.74% (0.331%) and 2.24% (0.325%), respectively; the LS mean difference between the HLX14 group and Prolia group was 0.50% (95% CI: −0.41%, 1.41%).

Based on the extension efficacy set, with the application of hypothesis strategy for handling ICEs, the mean (SD) percent changes from baseline to Week 78 in BMD at the femoral neck assessed by the Investigator for subjects in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups were 3.53% (4.568%), 3.28% (4.202%) and 2.25% (4.263%), respectively. Based on the MMRM, the LS mean (SE) percent changes from baseline to Week78 in BMD at the femoral neck assessed by the Investigator for subjects in the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups were 3.49% (0.301%), 3.21% (0.433%) and 2.36% (0.425%), respectively; the LS mean differences between the HLX14/HLX14 group and Prolia/Prolia group, and between the Prolia/HLX14 group and Prolia/Prolia group were 1.13% (95% CI: 0.11%, 2.16%) and 0.86% (95% CI: −0.34%, 2.05%), respectively.

In summary, with the application of hypothesis strategy for handling ICEs, percent changes from baseline to Week 26 or Week 52 in BMD at the femoral neck assessed by the Investigator were similar between the HLX14 and Prolia groups; percent change from baseline to Week 78 in BMD at the femoral neck assessed by the Investigator was similar among the HLX14/HLX14, Prolia/HLX14 and Prolia/Prolia groups.

Table 11-14 MMRM for Percent Changes from Baseline to Week 52 in BMD at Femoral Neck by Central Imaging (Intention-to-Treat Set)

Time Point	Statistic	HLX14 (N=256)	Prolia® (N=258)
Percent Changes from Baseline - Week 26 (%)	LS Mean (SE)[1]	2.35 (0.234)	2.06 (0.231)
	LS Mean 95% CI[1]	1.89, 2.81	1.60, 2.51
	LS Mean Difference (vs. Prolia) (95% CI)[1]	0.29 (-0.36, 0.94)	
	P-value	0.379	
Percent Changes from Baseline - Week 52 (%)	LS Mean (SE)[1]	2.67 (0.254)	2.05 (0.249)
	LS Mean 95% CI[1]	2.17, 3.17	1.56, 2.54
	LS Mean Difference (vs. Prolia) (95% CI)[1]	0.62 (-0.08, 1.32)	
	P-value	0.084	

Hypothesis strategy was mainly applied for intercurrent events (ICEs) such as premature treatment discontinuation before Week 26, use of prohibited drugs, and so on.

Ancillary analyses

Not applicable.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17. ***Summary of efficacy for trial HLX14-002-PMOP301 (Treatment period 1)***

Title: A Randomized, Double-blind, International Multicenter, Parallel-controlled Phase III Clinical Study to Evaluate Recombinant Anti-RANKL Human Monoclonal Antibody Injection (HLX14) versus Denosumab Injection (Prolia) in Postmenopausal Women with Osteoporosis at High Risk of Fracture.			
Study identifier	EudraCT Number: 2022-002188-31 Trial Registration Number: NCT05352516		
Design	It's a randomized, double-blind, international multicenter, parallel-controlled phase III clinical study to compare the efficacy, PD, PK, immunogenicity and safety of HLX14 vs. Prolia in postmenopausal women with osteoporosis at high risk of fracture.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		17 Jun 2022-19 Jan 2024 (Database Lock Date) not applicable 19 Jan 2024 – 03 June 2024
Hypothesis	Equivalence		
Treatments groups	HLX14 group		HLX14 N=256 Subjects received a total of 2 doses subcutaneous injection of HLX14 (60 mg/mL, Q6M), meanwhile taking at least 1000 mg of calcium daily and at least 400 IU of vitamin D daily (dose was adjusted by the investigator based on serum calcium) until the end of Week 52 or at premature withdrawal.
	Prolia group		Prolia N=258 Subjects received a total of 2 doses subcutaneous injection of Prolia (60 mg/mL, Q6M), meanwhile taking at least 1000 mg of calcium daily and at least 400 IU of vitamin D daily (dose was adjusted by the investigator based on serum calcium) until the end of Week 52 or at premature withdrawal.
Endpoints and definitions	Primary efficacy endpoint	Percent change from baseline in BMD at the lumbar spine to Week 52 (D365)	Percent change from baseline in bone mineral density at the lumbar spine to Week 52 (D365)
	Primary pharmacodynamics endpoint	$AUEC_{0-26W}$ of s-CTX	Area under the effect-time curve for percent change of serum type I collagen C-telopeptide (s-CTX) from baseline to Week 26 (D183) ($AUEC_{0-26W}$)
	Secondary efficacy endpoint	Fracture rate from baseline to Week 26, 52 (D183, D365)	Fracture rate from baseline to Week 26, 52 (D183, D365)

	Secondary efficacy endpoint	Percent change in BMD at lumbar spine, total hip, femoral neck from baseline to Week 26, 52 (D183, D365)	Percent change in bone mineral density at lumbar spine, total hip, femoral neck from baseline to Week 26, 52 (D183, D365)
	Secondary pharmacodynamics endpoint	Relative percent change in s-CTX from baseline to D15, D19, D57, D92, D106, D134, D162, D183, D274, D365	Relative percent change in serum type I collagen C-telopeptide from baseline to D15, D19, D57, D92, D106, D134, D162, D183, D274, D365
	Secondary pharmacodynamics endpoint	Relative percent change in s-P1NP from baseline to D15, D19, D57, D92, D106, D134, D162, D183, D274, D365	Relative percent change in serum procollagen type I N propeptide from baseline to D15, D19, D57, D92, D106, D134, D162, D183, D274, D365
Database	19 Jan 2024		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point	Intention-to-treat (ITT) set: Defined as all postmenopausal women with osteoporosis at high risk of fracture who were randomized in this study. Primary Analysis at week 52		
Descriptive statistics and estimate variability	Treatment group	HLX14 group	Prolia group
	Number of subjects	256	258
	Percent change from baseline in BMD at the lumbar spine to Week 52 (D365) (Mean)	6.10%	5.96%
	SD	3.928%	3.894%
	Fracture rate from baseline to Week 52 (D365)	3.9%	3.9%
	95% CI	(1.9%, 7.1%)	(1.9%, 7.0%)
	Percent change from baseline in BMD at the lumbar spine to Week 26 (D183) (Mean)	3.91%	4.48%
	SD	3.891%	3.509%
	Percent change in BMD at total hip from baseline to Week 26 (D183) (Mean)	2.47%	1.82%
	SD	2.665%	2.657%
	Percent change in BMD at total hip from baseline to Week 52 (D365) (Mean)	3.46%	2.58%
	SD	2.934%	3.085%

	Percent change in BMD at the femoral neck from baseline to Week 26 (D183) (Mean)	2.38%	2.02%
	SD	3.648%	3.588%
	Percent change in BMD at the femoral neck from baseline to Week 52 (D365) (Mean)	2.72%	2.01%
	SD	3.452%	4.179%
Effect estimate per comparison	Percent change from baseline in BMD at the lumbar spine to Week 52 (D365)	Comparison groups	HLX14 group vs. Prolia group
		LS Mean Difference between groups	0.21%
		95% CI	(-0.51%, 0.94%)
	Fracture rate from baseline to Week 52 (D365)	Comparison groups	HLX14 group vs. Prolia group
		Adjusted risk difference between groups	0.0%
		95% CI	(-3.3%, 3.4%)
	Percent change in BMD at lumbar spine from baseline to Week 26 (D183)	Comparison groups	HLX14 group vs. Prolia group
		LS Mean Difference between groups	-0.55%
		95% CI	(-1.22%, 0.12%)
	Percent change in BMD at total hip from baseline to Week 26 (D183)	Comparison groups	HLX14 group vs. Prolia group
		LS Mean Difference between groups	0.63%
		95% CI	(0.15%, 1.12%)
	Percent change in BMD at total hip from baseline to Week 52 (D365)	Comparison groups	HLX14 group vs. Prolia group
		LS Mean Difference between groups	0.89%
		95% CI	(0.35%, 1.44%)
	Percent change in BMD at the femoral neck from baseline to Week 26 (D183)	Comparison groups	HLX14 group vs. Prolia group
		LS Mean Difference between groups	0.29%
		95% CI	(-0.36%, 0.94%)
	Percent change in BMD at the femoral neck from baseline to Week 52 (D365)	Comparison groups	HLX14 group vs. Prolia group
		LS Mean Difference between groups	0.62%
		95% CI	(-0.08%, 1.32%)

Notes	The 95% CI for the difference of primary efficacy endpoint fell within the pre-specified equivalence margins (-1.45%, 1.45%), demonstrating the equivalence in clinical efficacy between HLX14 and Prolia.		
Analysis description	**Primary Pharmacodynamic Analysis**		
Analysis population and time point description	Pharmacodynamic set (PDS): All subjects who were randomized to receive at least one dose of study drug and had at least one post-administration PD concentration at the planned PD sample collection time point without significant protocol deviation from the evaluation of the s-CTX $AUEC_{0\text{-}26W}$. Primary Analysis at week 52		
Descriptive statistics and estimate variability	Treatment group	HLX14 group	Prolia group
	Number of subjects	234	237
	$AUEC_{0\text{-}26W}$ of s-CTX (day*%inhibition) (GeoMean)	14075.1253	13883.3613
	CVb%	17.3%	17.9%
	Relative percent change in s-CTX from baseline to D15 (Mean)	-86.55%	-86.35%
	SD	8.283%	8.805%
	Relative percent change in s-CTX from baseline to D29 (Mean)	-86.27%	-86.30%
	SD	9.410%	9.936%
	Relative percent change in s-CTX from baseline to D57 (Mean)	-86.66%	-86.55%
	SD	9.100%	8.786%
	Relative percent change in s-CTX from baseline to D92 (Mean)	-85.88%	-86.05%
	SD	9.174%	9.129%
	Relative percent change in s-CTX from baseline to D106 (Mean)	-85.18%	-84.36 %
	SD	10.022%	10.827%
	Relative percent change in s-CTX from baseline to D134 (Mean)	-81.77%	-80.15%
	SD	13.715%	14.572%
	Relative percent change in s-CTX from baseline to D162 (Mean)	-73.57%	-71.00%
	SD	20.736%	24.141%

	Relative percent change in s-CTX from baseline to D183 (Mean)	-63.62%	-59.22%
	SD	27.425%	45.182%
	Relative percent change in s-CTX from baseline to D274 (Mean)	-85.88%	-84.70%
	SD	9.390%	11.844%
	Relative percent change in s-CTX from baseline to D365 (Mean)	-61.57%	-57.80%
	SD	30.053%	35.220%
	Relative percent change in s-P1NP from baseline to D15 (Mean)	1.73%	3.87%
	SD	22.165%	29.576%
	Relative percent change in s-P1NP from baseline to D29 (Mean)	-25.65%	-25.47%
	SD	22.935%	18.529%
	Relative percent change in s-P1NP from baseline to D57 (Mean)	-61.41%	-62.05%
	SD	21.276%	17.417%
	Relative percent change in s-P1NP from baseline to D92 (Mean)	-74.95%	-75.83%
	SD	17.163%	13.618%
	Relative percent change in s-P1NP from baseline to D106 (Mean)	-76.91%	-77.37%
	SD	14.967%	12.940%
	Relative percent change in s-P1NP from baseline to D134 (Mean)	-77.28%	-75.56%
	SD	14.031%	15.135%
	Relative percent change in s-P1NP from baseline to D162 (Mean)	-75.44%	-73.81%
	SD	15.485%	15.570
	Relative percent change in s-P1NP from baseline to D183 (Mean)	-71.80%	-70.29%
	SD	17.722%	17.953%

	Relative percent change in s-P1NP from baseline to D274 (Mean)	-78.35%	-79.15%
	SD	16.452%	13.555%
	Relative percent change in s-P1NP from baseline to D365 (Mean)	-68.18%	-65.92%
	SD	19.715%	22.413%
Effect estimate per comparison	$AUEC_{0-26W}$ of s-CTX	Comparison groups	HLX14 group vs. Prolia group
		T/R Ratio	1.01
		95% CI	(0.98, 1.05)
	Relative percent change in s-CTX from baseline to D15	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-0.31%
		95% CI	(-1.63%, 1.01%)
		P-value	0.647
	Relative percent change in s-CTX from baseline to D29	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	0.15%
		95% CI	(-1.28%, 1.58%)
		P-value	0.834
	Relative percent change in s-CTX from baseline to D57	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-0.15%
		95% CI	(-1.49%, 1.20%)
		P-value	0.830
	Relative percent change in s-CTX from baseline to D92	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-0.05%
		95% CI	(-1.41%, 1.30%)
		P-value	0.940
	Relative percent change in s-CTX from baseline to D106	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-0.70%
		95% CI	(-2.24%, 0.84%)
		P-value	0.371
	Relative percent change in s-CTX from baseline to D134	Comparison groups	HLX14 group vs. Prolia group

		LS Mean difference between groups	-1.48%
		95% CI	(-3.77%, 0.81%)
		P-value	0.204
	Relative percent change in s-CTX from baseline to D162	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-1.95%
		95% CI	(-5.79%, 1.89%)
		P-value	0.319
	Relative percent change in s-CTX from baseline to D183	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-4.22%
		95% CI	(-10.75%, 2.31%)
		P-value	0.205
	Relative percent change in s-CTX from baseline to D274	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-1.12%
		95% CI	(-2.70%, 0.45%)
		P-value	0.161
	Relative percent change in s-CTX from baseline to D365	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-2.96%
		95% CI	(-8.72%, 2.79%)
		P-value	0.312
	Relative percent change in s-P1NP from baseline to D15	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-1.77%
		95% CI	(-6.95%, 3.41%)
		P-value	0.502
	Relative percent change in s-P1NP from baseline to D29	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	0.27%
		95% CI	(-3.52%, 4.07%)
		P-value	0.887
	Relative percent change in s-P1NP from baseline to D57	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	1.70%
		95% CI	(-1.80%, 5.20%)

		P-value	0.341
	Relative percent change in s-P1NP from baseline to D92	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	1.52%
		95% CI	(-1.03%, 4.06%)
		P-value	0.242
	Relative percent change in s-P1NP from baseline to D106	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	1.72%
		95% CI	(-0.43%, 3.87%)
		P-value	0.116
	Relative percent change in s-P1NP from baseline to D134	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-0.84%
		95% CI	(-3.06%, 1.38%)
		P-value	0.459
	Relative percent change in s-P1NP from baseline to D162	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-0.80%
		95% CI	(-3.17%, 1.57%)
		P-value	0.506
	Relative percent change in s-P1NP from baseline to D183	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-0.55%
		95% CI	(-3.23%, 2.14%)
		P-value	0.688
	Relative percent change in s-P1NP from baseline to D274	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	1.33%
		95% CI	(-0.96%, 3.62%)
		P-value	0.253
	Relative percent change in s-P1NP from baseline to D365	Comparison groups	HLX14 group vs. Prolia group
		LS Mean difference between groups	-1.11%
		95% CI	(-4.62%, 2.41%)
		P-value	0.537

Notes	The geometric LS mean ratio of $AUEC_{0\text{-}26W}$ of s-CTX for subjects in the HLX14 group vs. Prolia group was 1.01, whose 95% CI (0.98, 1.05) fell within the pre-specified equivalence margins (0.8, 1.25), demonstrating the PD equivalence between HLX14 and Prolia.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

HLX14-002-PMOP301 was a randomized, double-blind, international multicentre, parallel-controlled phase III clinical study to evaluate HLX14 vs. Prolia (INN: denosumab) in postmenopausal women with osteoporosis at high risk of fracture. Overall, the design of the study is acceptable and is generally in agreement with previous Scientific Advice received from EMA.

Full 52 Week double-blinded efficacy and safety comparability data were available at the submission of MAA, and an updated CSR with the completed study including Week 78 data was provided upon request. This was considered acceptable, as the CHMP does not require the data on interchangeability and therefore the 1-year efficacy, safety and immunogenicity data were considered adequate for the initial submission. To evaluate long-term comparability in efficacy and safety, the completed Week 78 clinical data was requested during the MA evaluation procedure as supportive data.

There are currently 2 applicable protocols (v 4.0 for EMA and v 5.0 for FDA) and corresponding SAPs. These 2 protocols overlap in terms of week 52 treatments and primary endpoints, but the latest version also contains the transition period and analysis methods required by FDA. Both protocol versions were made available for comparison and review; as the changes are only related to the confidence intervals and to the additional evaluations after Week 52, this does not raise any concerns.

Study population

Conducting a clinical efficacy and safety study in postmenopausal women with osteoporosis was endorsed in SA (EMA/SA/0000084242) and proposed study population was in general agreed upon. CHMP recommendations have, overall, been followed. The reference product Prolia is approved for the treatment of osteoporosis in postmenopausal women and in men with osteoporosis at increased risk of fractures. Female patients with postmenopausal osteoporosis (PMO) are considered the most sensitive population with respect to the approved indications. Inclusion of postmenopausal women with a T-score of ≤ -2.5 is in line with the state of art definition and WHO criteria of osteoporosis. The exclusion of patients with T-score below -4.0 is also endorsed to reduce inter-subject variability of PMO patients.

Prior use of bisphosphonates, age<60 (17 patients in the HLX14 group and 19 patients in the Prolia group) and >85 (2 patients in the HLX14 group and 1 patient in the Prolia group), and other than light smoking (1 patient in the HLX14 group and 3 patients in the Prolia group) was still possible for some patients, although fulfilling the exclusion criteria because scientific advice was provided, and the population restricted after study initiation. As the numbers of affected subjects were small and similar between groups, this will not be further pursued.

It is known that baseline bone mineral density (BMD) relates to age and the 10-year probability of major osteoporotic fractures starts to increase more rapidly after the age of about 65 years. The age range (60 to 80 years, both inclusive) may introduce heterogeneity to the study population, e.g. due to age-related comorbidities. Age was very evenly distributed between groups. No weight limits have

been set, but BMI [< 25, 25-30, > 30] was a stratification factor for randomisation, i.e. weight should be equally distributed between treatment arms.

Available literature suggests that smoking may be associated with a greater rate of bone loss, thus an impact on bone mass cannot be ruled out. Light smokers were allowed to participate in the study, however, only 5 (1%) of PMO patients were light smokers (2 in the HLX14 group and 3 in the Prolia group). Due to the low sample size, this is not further pursued.

The exclusion of patients that used medication for osteoporosis and medication affecting bone turnover is endorsed, as they may introduce unwanted heterogeneity. Previous use of biological therapy for osteoporosis (e.g. denosumab, romosozumab or other investigational biological agents) and cathepsin K inhibitor therapy was not allowed. Patients who had received bisphosphonates (oral or intravenous), fluoride and strontium prior to randomization were excluded from the study as they may have long-term effects on bone metabolism.

The study was conducted in China and Australia. There was only one White patient per group from a non-Asian region in the ITT set and most patients were from China and ethnically Han Chinese. The applicant provided an extrapolation report "Draft justification for generalizing results from a CCS conducted in an Asian (Chinese) population to a non-Asian (EU) population". Evidence from published studies was provided to support that Asian and non-Asian subjects with osteoporosis are similarly sensitive to denosumab. According to the SmPCs for Prolia and Xgeva, there is no impact of race/ethnicity on the response to denosumab from a clinical perspective. The data and evidence presented support that the similarity conclusion between the reference product Prolia and HLX14 derived in an Asian population does also apply to a non-Asian population.

Randomisation and blinding

Stratified block randomization was applied with a 1:1 randomisation ratio and a block size of 6. The stratification factors BMI [< 25, 25-30, > 30] and geographic region [Asian or non-Asian] are deemed appropriate. Age, prior bisphosphonate use (yes/ no) and baseline BMD T-score at the lumbar spine are also important prognostic factors. For the primary efficacy endpoint, stratification factors of BMI (< 25, 25-30, > 30) and the baseline BMD values were used as covariates in primary, sensitivity and supplementary analyses. Besides, the age (< 65 years, ≥ 65 years) and prior bisphosphonate use (yes/ no) were adjusted for in addition in one of the sensitivity analyses.

For the secondary efficacy and pharmacodynamic endpoints, stratification factors of BMI (< 25, 25-30, > 30) and the baseline values for corresponding measures were used as covariates.

This was a double-blind study. However, as the presentation of the study drugs were not identical in visual appearance, the trained clinical staff(s) responsible for study drug administration (e.g., nurse/physician, etc.) were designated as unblinded study site personnel and were not involved in any clinical or safety evaluations that were part of the blinded protocol or had other patient contact. The process of blinding was adequately described and is considered acceptable.

Description of trial intervention

During the Treatment Period 1, D1-D364, subjects received subcutaneous injections of HLX14 or Prolia 60mg on D1 and D183, as per the first randomization. During Treatment Period 2, subjects in the Prolia arm were rerandomized 1:1 to either receive a third dose of Prolia or transition to HLX14 and receive a single dose of HLX14. Subjects in the HLX14 arm continued to receive a third dose of HLX14.

The proposed dose of 60 mg SC on Day 1 of each 6-month cycle is the approved dose of the reference product Prolia for the treatment of postmenopausal osteoporosis and is considered sufficiently sensitive to detect potential differences between the biosimilar candidate and the originator. No dose adjustment was permitted for HLX14 or Prolia.

Concomitant and rescue therapies

Subjects received a daily supplement of oral calcium (at least 1000 mg) and vitamin D (at least 400 IU daily) from screening to end-of-study. Supplementation with calcium and vitamin D is adequate and in accordance with Prolia SmPC to prevent low serum calcium level while taking study drugs. Calcium and/or vitamin D supplementation could be adjusted at the discretion of the principal Investigator.

Drugs known or suspected to affect bone metabolism were prohibited during this study. The prohibited therapies were compared between treatment arms and clarified how the patients receiving prohibited therapies/rescue treatment were included in the primary analysis (see estimand).

Study assessments

Patients included in the study had at least 3 vertebrae in the L1-L4 region of lumbar spine and at least one hip evaluable by DXA, assessed by the central imaging.

BMD was measured by DXA. In all study procedures, the same DXA machine was used for the same subject, using the calculation results of the same sites. All DXA scans were submitted to the central imaging for analysis. After analysis by the central imaging, the study site was required to re-acquire scans due to improper location or other technical reasons, according to the requirements of the central imaging. A sensitivity analysis using BMD measurements from the Investigator/site was performed.

Primary objectives

The primary efficacy objective of this study was the demonstration of equivalence of HLX14 to Prolia in terms of percent change from baseline in lumbar spine bone mineral density at Month 12 in postmenopausal women with osteoporosis.

The primary PD objective of this study was the demonstration of equivalence in terms of area under the effect-time curve for percent change of serum type I collagen C-telopeptide (s-CTX) from baseline to Week 26 (D183) (AUEC0-26W) between HLX14 and comparator Prolia in postmenopausal women with osteoporosis at high risk of fracture.

Margin derivation

According to meta-analysis results (Bone HG, 2008; McClung MR, 2006; Cummings SR, 2009), the difference between Prolia and placebo in percent change in BMD from baseline in the proposed trial population was 5.35% (95% CI:4.83%, 5.87%). A margin of 1.45% between HLX14 versus EU-Prolia in Percent change from baseline in BMD at the lumbar spine was chosen as this would retain 70% of the minimum treatment effect of 4.83% relative to placebo (=3.38/4.83). Given the adequacy of the meta-analysis, the statistical justification ensures superiority to a putative placebo. The clinical justification is still missing and should explain which loss/excess in the change in BMD would still be considered clinically unimportant. However, when the originator product changed its manufacturing a few years ago, full comparability was requested by EMA. In the clinical study for approval, the lower and upper bounds of the same 2-sided 95% CI of the between group difference were compared with the equivalence margin of ±1.44% for assessing equivalence. As results are within ±1.44% a margin justification will not be further pursued.

The acceptance region of 80-125% for AUEC0-26W for percent change of s-CTX from baseline is based on margins used for conventional bioequivalence analyses as there is limited historical s-CTX data in the target population (women with PMO), and different bioanalytical assays and reagents may have been used. Further discussion would have been required if the point estimate or a substantive part of the confidence interval had lain towards the extremes of the acceptance criteria.

Primary estimands

The primary endpoints of study HLX14-002-PMOP301 were "%CfB in BMD for lumbar spine (L1 to L4) by DXA at Week 52" for efficacy and "AUEC of s-CTX over the initial 6 months (from Day 1 pre-dose to Week 26 pre-dose)" for PD.

Percent change from baseline in bone mineral density (BMD) for lumbar spine at month 12 is considered an acceptable endpoint. BMD has been demonstrated to correlate with vertebral fracture risk reduction with denosumab treatment. BMD has also been used as primary endpoint when Prolia was granted marketing authorization for men at increased risk of fractures (Prolia vs placebo, LS-BMD mean change after 12 months was 4.8%) [Prolia EPAR, 2010]. However, the causal link (surrogacy) between the marker and longer-term endpoints has not been unequivocally proven. (GUIDELINE ON THE EVALUATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF PRIMARY OSTEOPOROSIS, CPMP/EWP/552/95 Rev. 2). The incidences of new fractures during the study are investigated as secondary endpoints. Furthermore, BMD has a rather low dynamic range; changes in BMD are seen over months and years.

S-CTX is an accepted accurate marker of treatment effects of osteoporosis medications. The change in s-CTX occurs within days or weeks and prevails over several months (Cummings, 2009; Nakamura, 2011); data for this marker are also available for the reference product Prolia. Therefore, s-CTX might be more sensitive to compare test and reference product in terms of biosimilarity than assessment of BMD. However, the clinical relevance might be higher for BMD, which is often used in clinical trials. A comparison of s-CTX over the initial 6 months after the first dose was nominated as co-primary endpoint to BMD for its better dynamic response. Differences in bone turnover rates between individual patients may result in heterogeneous s-CTX levels. Hence, Emax may be more affected by inter-individual variability and AUEC is considered a more robust parameter to examine similarity. On the other hand, Emax could also be relevant as an endpoint, if a s-CTX threshold level exists, that correlates to actual physiological effects of bone resorption. Based on request, PD parameters of s-CTX and of s-P1NP in HLX14 and Prolia groups including AUEC0-26W, netAUEC0-26W (with rebound area being subtracted), Imin, Imax and Tmin were presented. The minimum concentration of s-P1NP is reached on average 6 days later for HLX14 than for Prolia. The AUEC0-26W and netAUEC0-26W is slightly lower for Prolia than for HLX14 for both s-CTX and of s-P1NP. It is agreed that no clinically relevant differences could be observed.

The intercurrent events include study discontinuation together with reason, prohibited drugs, changes in concomitant medication or bone-affecting interventions or AE's affecting bone (e.g. fractures). As mentioned in ICH E9.R1, estimands that are constructed with one or more intercurrent events accounted for using the treatment policy strategy present similar issues for non-inferiority and equivalence trials as those related to analysis of the FAS under the ITT principle. Responses in both treatment groups can appear more similar following discontinuation of treatment or use of another medication. Although a hypothetical strategy may be the most sensitive approach to detect any differences that are attributable to the pharmacological action, a treatment policy strategy would reflect clinical practice. The treatment policy and hypothetical strategy are considered to have equal importance in an equivalence setting and must lead to similar results for a robust interpretation.

For the BMD endpoint intercurrent events that occurred after treatment initiation and either precluded observation of the variable, or affect its interpretation, used a hypothetical strategy to estimate a treatment effect as if all subjects adhered to treatment until the primary analysis time point. A hypothetical strategy is applied for all intercurrent events except for "Injury, poisoning and procedural complications: spinal fracture, hip fracture and so on" where a treatment policy strategy is used. It is unclear how fractures will affect the primary BMD outcome, but as they are probably treatment related, a treatment policy strategy is acceptable. As a sensitivity analysis, a treatment policy strategy was applied for all intercurrent events, data collected after ICEs were used, and an MMRM applied. Both estimands are seen as equally important.

The BMD data of subjects with treatment discontinuation before Week 26 due to adverse event or lack of efficacy, or with new fractures (treatment related) that made it impossible to assess the lumbar BMD at week 52 (D365), were imputed using worst-observation-carried forward (WOCF), i.e. the worst (lowest) observed BMD value was selected in the observed values. This would be similar to a while-on-treatment strategy having the worst observed BMD within 52 weeks as primary endpoint. This should form a MNAR imputation ascribing an extreme unfavourable value. The applicant was asked to clarify how many BMD outcomes of patients needed to be imputed due to new fractures and for how many a treatment policy strategy could be applied. The applicant clarified that out of 20 subjects with new fractures the outcomes at Week 52 needed to be imputed for 2 subjects due to missing data and for 5 subjects due to other ICEs such as "did not take the 2nd dose on week 26" and "Use of Prohibited Drugs" occurring in addition. In total, the data of seven subjects were imputed, but never due to new fractures making it impossible to assess the lumbar BMD at week 52.

All other ICEs were multiple imputed based on MAR using the regression imputation model with baseline BMD and BMD from Week 26, baseline BMI (kg/m2) (<25, 25-30, >30), as terms in the model, by treatment group. Reliable reasons for discontinuation are difficult to ascertain, few or no treatment discontinuations might be truly independent from a perceived lack of efficacy or from safety reasons. Especially for use of prohibited drugs and non-drug intervention, the MAR assumption would not hold. However, also a tipping point multiple imputation analysis was applied: Missing Week 52 data was multiple imputed based on MAR, and for each arm a penalty was added to the imputed values at Week 52 where treatment related ICEs (premature treatment discontinuation due to any reason, use of prohibited drugs and treatment related fractures) happened. By request, the applicant performed a tipping point analysis for all BMD values imputed using a hypothetical strategy and all missing data. The conclusion (95% CI for the difference fell within the pre-specified equivalence margins) would be reversed only for a negative penalty of shift for Prolia decreases by 5% or more or shift for HLX14 decreases by 6% or more or a positive penalty of shift for Prolia increases by 7% or more or shift for HLX14 increases by 4% or more. Considering the observed BMD values, it is agreed that the needed penalty levels are exceedingly large and that the primary analysis results are robust even considering MNAR.

For the s-CTX endpoint a treatment policy strategy is used for all intercurrent events as they might not affect the PD, data collected after ICEs were used. As for the primary efficacy endpoint, also a hypothetical strategy should be applied for the primary PD endpoint. Several supplementary analyses are suggested which either add or exclude additional patients. However, these analyses do not form new estimands using a principal stratum strategy as the subset of subjects who experience an intercurrent event on the test treatment will often be a different subset from those who experience the same intercurrent event on control.

Secondary objectives and estimands

The secondary objectives included PK, PD, efficacy, safety and immunogenicity aspects of HLX14 and the reference product. Overall, the secondary objectives of the study are endorsed.

Secondary efficacy endpoints

The secondary efficacy endpoints consist of "Fracture rate from baseline to Week 52, and Week 78", "Percent changes in BMD at lumbar spine from baseline to Week 26, Week 78 (assessed by the central imaging)" and "Percent changes in BMD at total hip/the femoral neck from baseline to Week 26, Week 52, and Week 78". The secondary efficacy endpoints are considered clinically relevant as they are less sensitive to detect differences, but adequate to support the primary efficacy endpoint. Fracture rate is even more clinically relevant than BMD, which is acts as a surrogate marker of risk for fractures, but the number of fractures is expected to be limited because fractures are difficult to measure and can be unrelated to disease.

No precise definition of fracture was provided, and no differentiation was made between vertebral, nonvertebral and hip fractures (occurring at the site of femur neck, femur intertrochanter, or femur subtrochanter). It is unclear if pathologic fractures and fractures of the skull, facial bones, mandible, metacarpals, and phalanges of fingers or toes and fractures associated with severe trauma were excluded as they are not associated with decreased BMD. This is discussed in further detail in the safety section.

The comparison of the rates of intercurrent events are also endorsed, as demonstration of biosimilarity could be questioned if the rates of relevant intercurrent events differ between the trial arms. These intercurrent events include premature treatment discontinuation (due to AE, lack of efficacy and other reasons), bone-affecting interventions (use of prohibited drugs, non-drug intervention), AEs affecting bone (injury, poisoning and procedural complications, metabolism and nutrition disorders/endocrine disorders, gastrointestinal disorders, musculoskeletal and connective tissue disorders, nervous system disorders, other), and changes in concomitant medication. Summary of intercurrent events from baseline to Week 26 and Week 52 were presented for the different endpoints (see results section).

Secondary PD endpoints

EMA Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis (CPMP/EWP/552/95 Rev. 2, 2006) states that appropriate biochemical markers of bone turnover include osteocalcin, bone-specific alkaline phosphatase, urine and serum N- or C-telopeptide of type I collagen (s-NTX or s-CTX), and N-propeptide of type I procollagen (P1NP). The %CfB of s-CTX and of the anabolic marker P1NP at D15, D29, D57, D92, D106, D134, D162, D183 (within 7 days prior to the second dose), D274, D365 (within 7 days before the third dosing) and D547 (at the end-of-study visit) are included as additional secondary PD endpoints to enhance assessment of comparability of the biosimilar with the originator in terms of efficacy. Additional characterisation of PD markers after the second administration are very sparse. Overall, the secondary PD endpoints are considered acceptable to support the demonstration of PD similarity of HLX14 and EU-Prolia.

Secondary PK endpoints

The PK endpoint in this study was the serum drug concentration of the study drugs (HLX14 and comparator Prolia) at each time point. No further analyses on PK parameters were foreseen in this study and the PK sampling was also very sparse.

Statistical methods

Primary efficacy analyses

The analysis model for % BMD change was a linear regression (ANCOVA) of % BMD change with the treatment group as a fixed effect and stratification factors BMI (< 25, 25-30, > 30), and baseline BMD values as covariates. The following sensitivity analyses were applied: 1) MMRM instead of ANCOVA (still patients discontinuing due to either AE or to lack of efficacy and treatment related lumbar spine fracture, missing data was imputed by WOCF), 2) Tipping-point multiple imputation analysis, 3) treatment policy strategy for all intercurrent events and MMRM, 4) Using BMD measurement from the Investigator/site and 5) Added age (<65 years,>=65 years) and prior bisphosphonate use (yes/ no) in the multiple imputation and ANCOVA (also presented the results of using treatment policy strategy and MMRM model adding covariates). Using multiple imputation or an MMRM to impute under MAR should not make much difference. The regression imputation model with baseline BMD and BMD from Week 26, baseline BMI (kg/m2) (<25, 25-30, >30) as terms in the model by treatment group is considered adequate.

Secondary efficacy analyses

Missing values for secondary efficacy measures was imputed assuming MAR.

The *fracture rate from baseline to Week 52* was analyzed using the Cochran-Mantel-Haenszel (CMH) test to compare the two treatment groups taking into account the stratification (BMI [< 25, 25-30, > 30]). The relative risk/risk difference between two groups and its 95% CI were estimated. A hypothetical strategy is applied for all intercurrent events, data collected after ICE occurred was not used for analysis. While it is not fully clear how data were imputed, this is not further pursued for this secondary endpoint.

For the other continuous secondary efficacy measures (*percent change in BMD at the lumbar spine, at total hip and at the femoral neck*), a similar strategy for intercurrent events as for the primary endpoint is used (a hypothetical strategy for all intercurrent events except for the treatment policy strategy for lumbar spine fracture for the lumbar spine BMD endpoint). For total hip/femoral neck BMD endpoints, also a hypothetical strategy was applied for patients with total hip or femoral neck fracture.

Primary PD analyses

The between-group least squares means (LSMs), geometric mean ratio (GMRs), and its 95% CI for AUEC0-26W were calculated by ANOVA using the treatment groups as fixed factor. As it was unclear why the analysis was not adjusted for important prognostic factors, clarification was requested. The applicant clarified that the original primary PD analysis on PDS was with a treatment strategy for ICEs and no imputation for missing PD data. The requested sensitivity PD analysis was performed adjusting for weight, prior bisphosphonates therapy (Yes versus No) and baseline s-CTX level as covariates: The ratio of geometric LS mean of AUEC0-26W for s-CTX in HLX14 and Prolia groups was 1.01 (95% CI: 0.98, 1.04). It is agreed that this result is in line with the result of the original ANOVA analysis without covariates (GMR: 1.01; 95%CI: 0.98, 1.05).

Several supplementary analyses were performed: 1) an analysis on the ITT set without imputing for missing data, 2) an analysis on the PDS excluding patients with W0-26 ICEs affecting AUEC0-26w, that was patients with W0-26 ICEs (bone-affecting interventions, adverse events affecting bone, and changes in concomitant medication) and patient's AUEC0-26W deviation from the mean AUEC0-26W of all subjects were greater than 20% and 3) an analysis on the PDS with patients with W0-26 ICEs or not meeting with Inclusion and Exclusion Criteria excluded. Excluding patients with ICEs or missing data could be very similar to the primary analysis method depending on the handling of missing data and definition of protocol violations leading to the exclusion from PDS. Excluding patients with large AUEC0-26W deviation from the mean AUEC0-26W of all subjects is not supported as this will make both treatments appear more similar. A hypothetical strategy for intercurrent events was already suggested above.

Secondary PD analyses

Based on the PDS, an MMRM was used for the repeatedly measured continuous variables %CfB of s-CTX and s-P1NP to calculate the adjusted means of the changes from baseline in these groups together with standard error. A treatment policy strategy is applied for all intercurrent events and missing data is automatically imputed under MAR. This is acceptable for secondary endpoints.

<u>Planned subgroup analyses</u>

Subgroup analyses for age (< 60, ≥ 60, ≤ 85, > 85 and < 65, ≥ 65), BMI (< 25, 25 – 30, > 30), Geographic region (Asian or non-Asian), Prior use of bisphosphonates (Y, N) and Smokers (non-smokers, light smokers, other) were planned on the ITT set for all primary and secondary efficacy endpoints.

Efficacy data and additional analyses

The study started on 17-Jun-2022, and the primary endpoint was completed to be measured for all patients on 17-Dec-2023. Upon request, the applicant provided the final CSR including data from the transition period/treatment period 2 up to week 78, for which the database lock date was 03-July-2024. The study was completed on 05-June-2024. Full 52 Week double-blinded efficacy and safety comparability data were available at the submission of MAA.

Changes in the planned conduct of the study

The original protocol, HLX14-002-PMOP301 V1.0, dated 10 Sep 2021, was amended 4 times (V2.0 (15 Mar 2022), V3.0 (18 Jul 2022), V4.0 (02 Nov 2022), V5.0 (03 Mar 2023)), 3 times after study start on 17-Jun-2022. The listed major changes between protocols did not raise any concerns and were mainly based on previous scientific advice.

Participant flow and numbers analysed

Treatment period 1

Of the 1078 screened subjects, 514 subjects were randomized in a 1:1 ratio. All 514 subjects received study treatment. The reasons for screen failures were not presented.

Among the randomized subjects, 471 (91.6%) subjects (HLX14 group vs. Prolia group: 234 [91.4%] vs. 237 [91.9%]) completed the treatment of Week 26, and 477 (92.8%) subjects (235 [91.8%] vs. 242 [93.8%]) completed the study (i.e., completed the Week 52 visit). As there were only 2 doses in treatment period 1, discontinuation before Week 26 is called treatment discontinuation and discontinuation before Week 52 study discontinuation. It is unclear if all patients discontinuing treatment also discontinued the study. Main reason for treatment and study discontinuation was withdrawal of informed consent (10 vs 11 patients and 11 vs 11 patients). Other reasons for treatment and study discontinuation were poor compliance (3 vs 0 patients and 2 vs 1 patients), subject decision (7 vs 9 patients and 5 vs 3 patients) and lost to follow-up (2 vs 0 patients and 2 vs 0 patients). Thus, the number of subjects completing the main period was high. In addition, the number of subjects discontinuing the study and reasons for discontinuation were similar between the groups.

Treatment period 2

On day 365, 220 patients in the Prolia group were re-randomised to receive either Prolia (Prolia/Prolia) or HLX14 (Prolia/HLX14) in a 1:1 ratio, and 220 patients in the HLX14 group continued to receive HLX14 (HLX14/HLX14). All 440 subjects continuing into the second treatment period received the third, additional dose. 5 subjects overall (1 in the HLX14/HLX14, 2 in the Prolia/HLX14, and 2 in the Prolia/Prolia group) were discontinued from the study due to poor compliance, failure to attend follow-up, subject decision, and withdrawal of inform consent prior to week 78. The overall proportion of subjects who completed the study is high (98.9%) and therefore raises no concerns.

Analysis sets

All efficacy endpoints were analysed based on the ITT set and the PPS as supplementary analyses.

All 514 subjects were included in the ITT set and SS; 459 (89.3%) subjects (225 [87.9%] vs. 234 [90.7%]) were included in the PPS; 506 (98.4%) subjects (252 [98.4%] vs. 254 [98.4%]) were included in the PKS; 471 (91.6%) subjects (234 [91.4%] vs. 237 [91.9%]) were included in the PDS.

The differentiation between major protocol deviations (48.2% in total, 50.8% in the HLX14 group and 45.7% in the Prolia group) and important protocol deviations (7% in total, 8.2% in the HLX14 group and 5.8% in the Prolia group) is unclear, especially which protocol deviations were excluded from the PPS. Major protocol deviations were mainly due to visit schedule (94 vs 98 patients),

inclusion/exclusion criteria (32 vs 22 patients), procedures/tests (21 vs 17 patients), disallowed medications (16 vs 11 patients) and IP Admin/Study Treat (13 vs 10 patients). Approximately half of visit schedule major protocol deviations can be explained by COVID 19. Important protocol deviations were mainly due to visit schedule (5 vs 9 patients), disallowed medications (8 vs 4 patients), IP Admin/Study Treat (8 vs 3 patients) and inclusion and exclusion criteria (2 vs 0 patients). Important PDs were the protocol deviations that significantly affected the primary efficacy assessment and leading subjects to be excluded from PPS. There was a large number of major protocol deviations related to COVID 19 (18.7%) but equally distributed between groups.

The ITT set consisted of 514 patients (256 in the HLX14 group and 258 in the Prolia group) whereas the PPS consisted of 459 patients (225 in the HLX14 group and 234 in the Prolia group), i.e. 31 patients in the HLX14 group and 24 patients in the Prolia group were excluded from the PPS. Main reasons were that subjects did not take the second dose, took a prohibited drug (8 patients in the HLX14 vs 4 patients in the Prolia group), met an exclusion criterion (2 patients in the HLX14 group) or took the second dose earlier than scheduled (1 patient in the HLX14 group). The higher number of patients being excluded due to a prohibited drug is noted.

The PKS consisted of 506 patients (252 in the HLX14 group and 254 in the Prolia group), 4 patients per group were excluded due to no post-dose serum concentration at a scheduled sampling time point.

The PDS consisted of 471 patients (234 in the HLX14 group and 237 in the Prolia group), 21 patients per group were excluded as subject's s-CTX AUEC cannot be calculated due to missing blood sample collection on Day 183, 1 patient in the HLX14 group was excluded due to the early administration of the second dose long before Day 183.

PDS is defined as all subjects who were randomized to receive at least one dose of study drug and had at least one post-administration PD concentration at the planned PD sample collection time point without significant protocol violation or deviation from the evaluation of the s-CTX AUEC0-26W.

The 'extension informed consent form set' consisted of all patients who signed ICF based on protocol version 5.0 (n=455) and the extension efficacy set (n=428), i.e. subjects receiving 1 dose of extension treatment and have one DXA measurement after Week 52 treatment.

Intercurrent events

Concerning the intercurrent events from baseline to Week 52, there was only one treatment discontinuation due to Adverse Event and this was in the Prolia group. No patient discontinued treatment due to lack of efficacy before Week 26. Overall, 42 patients discontinued treatment due to other reasons before Week 26 (22 in the HLX14 group and 20 in the Prolia group). The number of patients who used prohibited drugs was somewhat higher in the HLX14 than in the Prolia group but was low (8 patients in the HLX14 group and 4 patients in the Prolia group). There were no non-drug interventions. Overall, there were 12 fractures at the spine, 5 in the HLX14 group and 7 in the Prolia group. There was one fracture at femoral neck in the HLX14 group and none in the Prolia group. Non-fracture disorders affecting bone were observed in 3 patients in the HLX14 group and 7 in the Prolia group. Changes in concomitant medication occurred in 3 patients in the HLX14 group and 2 patients in the Prolia group.

Concerning the intercurrent events from baseline to Week 26, there were overall 21 ICEs, 13 in the HLX14 group and 8 in the Prolia group. More patients used prohibited drugs in the HLX14 group (5 patients) than in the Prolia group (2 patients). One more fracture was observed in the HLX14 group compared to the Prolia group (4 vs 3). Non-fracture disorders and changes in concomitant medication was equal between arms (2 patients per arm per category).

In treatment period 2, 5 subjects discontinued treatment: 1 in the HLX14-HLX14 group (poor compliance), 2 in the Prolia-HLX14 group (poor compliance, subject decision), and 2 in the Prolia-Prolia group (withdrawal of informed consent, subject decision).

Primary efficacy results

Primary efficacy analysis

Based on the ITT set, the mean (SD) percent change from baseline to week 52 in BMD at the lumbar spine assessed by central imaging for subjects in the HLX14 and Prolia groups were 6.10% (3.928%) and 5.96% (3.894%), respectively. The LS mean difference adjusted for baseline BMD values and stratification factor BMI (< 25, 25–30, > 30) using ANCOVA model between the HLX14 group and Prolia group was 0.21% (95% CI: -0.51%, 0.94%). The 95% CI for the difference fell within the pre-specified equivalence margins (-1.45%, 1.45%).

Results were even more similar for the PPS analysis. Based on the PPS, at Week 52, the LS mean difference between the HLX14 group and Prolia group was 0.10% (95% CI: -0.62%, 0.83%).

The Figure showing the percent change from baseline against time shows that at Week 26 HLX14 was below Prolia and the curves cross before Week 52 leading to numerically higher values for HLX14.

Sensitivity analyses for the primary endpoint

All sensitivity results were consistent with the primary analysis conclusion. Point estimates are in favour of HLX14 except when using BMD measurement from the Investigator and all results are within the pre-defined equivalence margin of 1.45%.

Secondary efficacy results

Fracture rate from baseline to Week 52, Week 78

Based on the ITT set, from baseline to Week 52, 10 (3.9%) subjects per group experienced new fractures. The adjusted risk difference between the HLX14 group and Prolia group was 0.0 (95% CI: -3.3%, 3.4%). The relative risk between the HLX14 group and Prolia group was 1.00 (95% CI: 0.97, 1.04).

Based on the PPS, from baseline to Week 52, the number of subjects experiencing new fracture were 7 (3.1%) and 6 (2.6%) in the HLX14 and Prolia groups, respectively. The absolute risk difference between the HLX14 group and Prolia group was 0.5% (95% CI: -2.5%, 3.6%); the adjusted risk difference between the HLX14 group and Prolia group was 0.6% (95% CI: -2.5%, 3.6%). The sensitivity analysis based on the ITT set, applying a hypothetical strategy, without considering stratification factors and the sensitivity analysis applying the treatment policy strategy for all ICEs led to the same results. Sensitivity analysis based on the ITT set, applying a hypothetical strategy, and for ICE treatment discontinuation due to lack of efficacy and AE used "fracture occurs" imputation led to one more fracture in the Prolia group.

Based on the extension efficacy set, with the application of hypothesis strategy for handling ICEs, from baseline to Week 78, 13 (6.0%), 8 (7.6%) and 6 (5.6%) subjects experienced new fractures in the HLX14-HLX14, Prolia-HLX14 and Prolia-Prolia groups, respectively, which is comparable.

The risk for subjects experiencing new fracture from baseline to Week 52 and Week 78 was similar between the two treatment groups.

Percent change in BMD at lumbar spine from baseline to Week 26, Week 78

Based on the ITT set, at Week 26, the LS mean (SE) percent change from baseline in BMD at the lumbar spine assessed by central imaging using MMRM for subjects in the HLX14 and Prolia groups

were 3.90% (0.242%) and 4.45% (0.238%), respectively; the LS mean difference between the HLX14 group and Prolia group was -0.55% (95% CI: -1.22%, 0.12%).

All sensitivity analyses based on the PPS, using a treatment policy for all ICEs and using BMD measurement from the Investigator showed comparable results. The point estimates at Week 26 are negative while at Week 52 they are positive (except for BMD measurement from the Investigator).

Based on the Extension Efficacy set, at week 78, the LS mean (SE) differences in percent change from baseline in BMD at the lumbar spine were assessed by central imaging using MMRM for HLX14/HLX14 and Prolia/HLX14 vs. Prolia/Prolia were 0.63 (95% CI: -0.40, 1.66) and 0.73 (95% CI: -0.47, 1.93). Observed differences were not statistically significant.

Percent changes in BMD at total hip from baseline to Week 26, Week 52, and Week 78

Based on the ITT set and the MMRM, at Week 26 the LS mean difference in percent change in BMD at total hip from baseline between the HLX14 group and Prolia group was 0.63% (95% CI: 0.15%, 1.12%). At Week 52, the LS mean difference in percent change in BMD at total hip from baseline between the HLX14 group and Prolia group was 0.89% (95% CI: 0.35%, 1.44%). Therefore, the LS mean difference in percent change in BMD at total hip from baseline was even statistically significant which is confirmed by most sensitivity analyses. However, results are in favour of HLX14 and still within the equivalence margin of 1.45% (except when using BMD measurement from the Investigator for Week 52: upper bound of the 95% CI 1.50%). All other sensitivity analyses based on the PPS and using a treatment policy for all ICEs showed comparable results.

Based on the Extension Efficacy set and the MMRM, at week 78 the LS mean differences in percent change from baseline in BMD at total hip between the HLX14/HLX14 and Prolia/HLX14 vs. Prolia/Prolia groups were 0.98 (95% CI: 0.3, 1.66, p=0.005) and 0.79 (95% CI: 0.00, 1.58; p=0.050). Although the comparison of HLX14/HLX14 vs. Prolia/Prolia in percent change from total hip were statistically significant, this does not raise concerns, as the results are statistically significant.

Percent changes in BMD at the femoral neck from baseline to Week 26, Week 52, and Week 78

Based on the ITT set and the MMRM, at Week 26, the LS mean difference in percent change from baseline in BMD at the femoral neck from baseline between the HLX14 group and Prolia group was 0.29% (95% CI: -0.36%, 0.94%). At Week 52, the LS mean difference percent change in BMD at the femoral neck from baseline between the HLX14 group and Prolia group was 0.62% (95% CI: -0.08%, 1.32%).

Similar as for Percent changes in BMD at total hip, when using BMD measurement from the Investigator for the difference in percent change in BMD at the femoral neck from baseline the upper bound of the 95% CIs are worse and near the margin of 1.45% at Week 52, but for femoral neck results are not statistically significant. All other sensitivity analyses based on the PPS and using a treatment policy for all ICEs showed comparable results.

Based on the Extension Efficacy set, and the MMRM, at week 78 the LS mean differences in percent change from baseline in BMD at the femoral neck between the HLX14/Prolia and Prolia/HLX14 groups vs. the Prolia/Prolia group were 0.73 (95% CI: -0.14, 1.60) and 0.46 (-0.55, 1.47). The results are not statistically significant, in favour of HLX14, and are therefore not considered concerning.

2.5.7. Conclusions on the clinical efficacy

The primary efficacy analysis based on the %CfB in LS-BMD at Week 52 was successful in demonstrating similarity, as the 95% CI of the difference between the HLX14 and the US-Prolia group fell within the pre-specified equivalence margins. Additionally, the primary PD endpoint (AUEC of s-CTX

over the initial 6 months) was met. Thus, the provided efficacy data support the biosimilarity of HLX14 and US-Prolia.

2.5.8. Clinical safety

The safety of HLX14 was evaluated in a PK and PD study in healthy adult male subjects (Study HLX14-001) and in an integrated PK, PD, confirmatory efficacy, safety, and immunogenicity study in female subjects with PMO (Study HLX14-002-PMOP301), who received at least one dose of HLX14 or Prolia. The comparator drugs in Study HLX14-001 were EU-Prolia and US, or CN-sourced Prolia. The comparator drug in Study HLX14-002-PMOP301 was EU-Prolia.

Protocol Number	Study Objectives	Subjects	Treatments Administered	Safety Variables
HLX14-001 Phase I	Compare the PK, PD, safety, tolerability, and immunogenicity of HLX14 and EU-Prolia®. Primary Objective: *Part I of the Study* To compare the PK parameters of HLX14 and EU-Prolia® in healthy adult male subjects to further provide basis for the study design of part II. *Part II of the Study* To compare the PK similarity of HLX14 and Prolia® (US, EU, and CN-sourced) in healthy adult male subjects.	Part I of the Study: A total of 24 healthy male subjects were planned to be enrolled, with 12 subjects in each group. The actual number of enrolled subjects was consistent with the planned number of enrollments, and a total of 24 subjects were actually enrolled, with 12 subjects in each group. Part II of the Study: A total of 228 healthy male subjects were planned to be enrolled, with 57 subjects in each group. A total of 228 healthy male subjects were actually enrolled, 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.	Single dose of HLX14 (60 mg/mL) or EU-Prolia® (60 mg/mL) Single dose of HLX14 (60 mg/mL) or US, EU, or CN-sourced Prolia® (60 mg/mL)	AEs, SAEs, other significant AEs (injection site reaction, AEs leading to drug interruption, AEs leading to drug discontinuation, and adverse events of special interest [AESIs]), clinical laboratory (including hematology, serum chemistry, urinalysis), physical examination, vital signs, and 12-lead ECG.
HLX14-002-PMOP301 Phase III	Clinical efficacy, PD, safety, PK, and immunogenicity. Primary Objective: To assess the equivalence of the primary clinical efficacy endpoint and primary PD endpoint between HLX14 and comparator Prolia® in postmenopausal women with osteoporosis at high risk of fracture.	A total of 478 postmenopausal women with osteoporosis at high risk of fracture were planned to be enrolled, with 239 subjects in each group. A total of 514 postmenopausal women with osteoporosis at high risk of fracture were actually enrolled, with 256 subjects in the HLX14 group and 258 subjects in the Prolia® group.	A total of 2 doses of HLX14 or Prolia® (60 mg/mL, once every 6 months)	AEs, SAEs, other significant AEs (injection site reaction, AEs leading to drug interruption, AEs leading to drug discontinuation, and AESIs), physical examination, vital signs, laboratory tests (including hematology, serum chemistry, urinalysis, coagulation function, 25-OH vitamin D), and 12-lead ECG.

The safety profile of the reference product denosumab is well established (Prolia SmPC, Prolia USPI, Xgeva SmPC, and Xgeva USPI). To account for the important known risks of hypocalcemia and ONJ, special precautions were taken in both clinical studies.

The Prolia and Xgeva product information recommend correction of pre-existing hypocalcemia by adequate intake of calcium and vitamin D before initiating denosumab therapy, as well as clinical monitoring of calcium levels before each dose and throughout treatment.

In accordance with the label recommendations, the following measures were taken:

- Subjects with hypocalcemia or vitamin D deficiency were excluded from study participation.

- Subjects received supplementation with calcium and vitamin D of at least:
    - Study HLX14-001: 600 mg/day calcium and 400 IU/day vitamin D from Days 1 to 134
    - Study HLX14-002-PMOP301: ≥1000 mg/day calcium and ≥400 IU/day vitamin D from Screening to EOS.
- Monitoring of calcium levels was done at regular intervals.

Both studies also excluded subjects with a history or presence of ONJ. Subjects with active dental or jaw condition that required oral surgery or those with planned invasive dental procedure were also excluded from both studies.

No pooling of safety data was performed as Study HLX14-001 was conducted in healthy male subjects and Study HLX14-002-PMOP301 in female subjects with PMO.

In study HLX14-001 safety assessments included AEs and SAEs, Physical examinations, vital signs (blood pressure, pulse rate, temperature), injection site reactions, laboratory tests (hematology, serum chemistry, and urinalysis) and 12-lead electrocardiography (ECG). Furthermore, ADA and NAb formation against HLX14 and Prolia (US, EU and CN) was evaluated.

The safety and immunogenicity endpoints in Study HLX14-001 were:

Safety:

- Incidence of AEs, SAEs, related AEs (including AEs based on ISRs, vital signs, ECG, and laboratory safety parameters)
- Proportion of subjects testing positive of anti-drug antibody (ADA) and neutralizing antibody (NAb).

The following analysis sets were used for analyses of disposition and baseline variables and safety data in Study HLX14-001:

- Full analysis set (FAS): included all randomised subjects
- Safety analysis set (SS): included all subjects who were randomised and received the study drugs

In Study HLX14-002-PMOP301, safety assessments after dosing consisted of AEs and SAEs, ISRs, vital signs (blood pressure, pulse rate, respiratory rate and body temperature), physical examination, ECG, and clinical laboratory tests (hematology, chemistry, urinalysis, coagulation Vitamin D and calcium). Furthermore, ADA and NAb formation against HLX14 and Prolia was evaluated.

The safety and immunogenicity endpoints in Study HLX14-002-PMOP301 were:

- Incidences of AEs and SAEs, laboratory tests (hematology, serum chemistry, urinalysis, etc.), ECG, physical examinations, vital signs
- Proportion of subjects testing positive for anti-drug antibodies (ADA) and neutralizing antibodies (NAb) to the study drugs.

The following analysis sets were used for analyses of disposition and baseline variables and safety data in Study HLX14-002-PMOP301:

- Intention-to-treat (ITT) set: all postmenopausal women with osteoporosis at high risk of fracture who were randomized in this study.
- Per protocol set (PPS): PPS was a subset of ITT set, and PPS was consisted of all subjects randomized without major protocol deviations that significantly affected the primary efficacy

assessment. The specific definition of PPS was confirmed before database lock. As a supportive analysis, the analysis based on the PPS complemented the analysis based on the ITT set.

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

2.5.8.1. Patient exposure

Exposure data are available for the following studies and populations:

Table 18. Number of subjects who received at least 1 dose of study drug (HLX14 or Prolia) in the HLX14 clinical studies: Safety Set (SS)

Study	Subjects	Amount of exposure	Number of subjects who received ≥ 1 dose of study drug				
			HLX14	EU-Prolia	US-Prolia	CN-Prolia	Total
Study HLX14-001 Part I	Healthy subjects	Single dose	12	12			24
Study HLX14-001 Part II		Single dose	58	56	57	57	228
Study HLX14-002-PMOP301	PMO Patients	Single dose	22	21			43
		Total 2 doses	234	237			471
total		**At least 1 dose**	326	326	57	57	766

Subject disposition

Study HLX14-001

Part I:

A total of 155 healthy adult male subjects were screened, of which 24 subjects were enrolled and randomized.

All 24 (100%) subjects were treated and completed the study, including 12 subjects in the HLX14 group and 12 subjects in the EU-Prolia group.

All the subjects (24 [100%]) enrolled in part I of the study were included in the FAS and SS.

Table 19. Disposition of subjects study HLX14-001 in part I (all screened subjects)

	HLX14 (N=12)	EU-Prolia® (N=12)	Total (N=24)
Subjects Screened			155
Screen Failure			117 (75.5)
Randomization, n (%)	12 (100)	12 (100)	24 (100) [1]
Subjects Treated, n (%)	12 (100)	12 (100)	24 (100)
Subjects not Treated, n (%)	0	0	0
Completed Study, n (%)	12 (100)	12 (100)	24 (100)
Discontinued from Study, n (%)	0	0	0
Reason for Discontinuation, n (%)			
Consent Withdrawal	0	0	0

	HLX14 (N=12)	EU-Prolia® (N=12)	Total (N=24)
Subjects Screened			155
Screen Failure			117 (75.5)
Randomization, n (%)	12 (100)	12 (100)	24 (100) [1]
Subjects Treated, n (%)	12 (100)	12 (100)	24 (100)
Subjects not Treated, n (%)	0	0	0
Completed Study, n (%)	12 (100)	12 (100)	24 (100)
Discontinued from Study, n (%)	0	0	0
Reason for Discontinuation, n (%)			
Consent Withdrawal	0	0	0

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.

All 228 (100%) subjects were 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%).

Among the 228 subjects enrolled in part II of the study, all (228 [100%]) subjects were included in FAS and SS.

Table 20. Disposition of subjects study HLX14-001 in Part II (all screened subjects)

	HLX14	US-Prolia®	EU-Prolia®	CN-Prolia®	Total
Subjects Screened					1030
Screen Failure					802 (77.9)
Randomization, n (%)	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
Subjects Treated, n (%)	58 (100)	57 (100)	56 (100)	57 (100)	228 (100)
Subjects not Treated, n (%)	0	0	0	0	0
Completed Study, n (%)	54 (93.1)	53 (93.0)	53 (94.6)	53(93.0)	213 (93.4)
Discontinued from Study, n (%)	4 (6.9)	4 (7.0)	3 (5.4)	4(7.0)	15 (6.6)
Reason for Discontinuation, n (%)					
Consent Withdrawal	0	0	0	0	0
Adverse Event	0	0	0	0	0
Death	0	0	0	0	0
Physician Decision	0	0	0	0	0
Poor Compliance and Fails to Attend Follow-up in Time	1 (1.7)	2 (3.5)	1 (1.8)	2 (3.5)	6 (2.6)
Serious Protocol Violation	0	0	0	0	0
Study Terminated by Regulatory Authorities	0	0	0	0	0
Study Terminated by Sponsor	0	0	0	0	0
Lost to Follow-up	1 (1.7)	0	1 (1.8)	0	2 (0.9)
Subject Refuse to Continue the Study	2 (3.4)	2 (3.5)	1 (1.8)	2 (3.5)	7 (3.1)

Percentage of screen failure is calculated using the number of screened subjects as denominator and other percentages are calculated using the number of randomized subjects as denominator.

Study HLX14-002-PMOP301

A total of 1078 subjects were screened, and 514 subjects were randomized to the HLX14 group (256 subjects) or the Prolia group (258 subjects). All 514 subjects received the study treatments. Among the randomized subjects, 471 (91.6%) subjects (HLX14 group vs. Prolia group: 234 [91.4%] vs. 237 [91.9%]) completed the treatment of Week 26, and 477 (92.8%) subjects (235 [91.8%] vs. 242 [93.8%]) completed the study (i.e., completed the Week 52 visit).

All 514 subjects were included in the ITT set and SS.

Table 21. Disposition of subjects study HLX14-002-PMOP301 (all screened subjects)

	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects screened			1078
Screen failure			564
Randomization[1], n (%)	256 (100)	258 (100)	514 (100)
Subjects treated[1], n (%)	256 (100)	258 (100)	514 (100)
Subjects not treated, n (%)	0	0	0
Completed Week 26 treatment[2], n (%)	234 (91.4)	237 (91.9)	471 (91.6)
Discontinued from treatment before Week 26[2], n (%)	22 (8.6)	21 (8.1)	43 (8.4)
Reason for discontinuation, n (%)			
Adverse Event	0	1 (0.4)	1 (0.2)
Lack of Efficacy	0	0	0
Withdrawal of Inform Consent	10 (3.9)	11 (4.3)	21 (4.1)
Lost to Follow-up	2 (0.8)	0	2 (0.4)
Death	0	0	0
Physician Decision	0	0	0
Poor Compliance	3 (1.2)	0	3 (0.6)
Serious Protocol Violation	0	0	0
Subject Decision	7 (2.7)	9 (3.5)	16 (3.1)
Other	0	0	0
Completed study on Week 52[3], n (%)	236 (92.2)	242 (93.8)	478 (93.0)
Discontinued from study before Week 52, n (%)	20 (7.8)	16 (6.2)	36 (7.0)
Reason for discontinuation, n (%)			
Withdrawal of Inform Consent	11 (4.3)	11 (4.3)	22 (4.3)
Adverse Event	0	1 (0.4)	1 (0.2)
Lack of Efficacy	0	0	0
Lost to Follow-up	2 (0.8)	0	2 (0.4)
Death	0	0	0
Physician Decision	0	0	0
Poor Compliance and Fails to Attend Follow-up in Time	2 (0.8)	1 (0.4)	3 (0.6)
Serious Protocol Violation	0	0	0
Study Terminated by Regulatory Authorities	0	0	0
Study Terminated by Sponsor	0	0	0
Subject Decision	5 (2.0)	3 (1.2)	8 (1.6)
Other	0	0	0

N: The number of subjects randomized; n: The number of subjects in specific category; %: (n/N*100).
[1] Stratified block randomization was used to randomize the eligible subjects to the experiment group (HLX14) or the control group (Prolia®) at 1:1 based on stratification factors BMI (< 25, 25-30, > 30) and geographic region (Asian or non-Asian). Subjects received subcutaneous injection of HLX14 or Prolia® 60 mg on D1 and D183.
[2] Completed Week 26 Treatment means subjects completed Week 26 dose. Discontinued from treatment before Week 26 summaries subjects who did not complete Week 26 dose.
[3] Completed study on Week 52 means subjects completed visit Week 52.
This protocol allowed rescreening of subjects who failed to enrollment. A total of 12 subjects were rescreened just one more time, 9 subjects were enrolled after rescreening, and 3 subjects were still failed to be enrolled. The number of "Subjects screened" and "Screen failure" included rescreened subjects.

Demographics and baseline characteristics

The demographics and baseline characteristics of Studies HLX14-001 and HLX14-002-PMOP301 are described above in the pharmacology and efficacy section, respectively.

Concomitant medications or Procedures

The frequency and pattern of use of concomitant medications were similar across HLX14 and Prolia groups (182 [71.1%] vs. 181 [70.2%]). The most frequently used drugs were anti-inflammatory and antirheumatic products, cough and cold preparations, and antibacterials for systemic use.

Similar numbers of subjects in the HLX14 and Prolia groups (26 [10.2%] vs. 28 [10.9%]) received concomitant procedures. These were surgical and medical procedures and investigations.

2.5.8.2. Adverse events

Adverse drug reactions

Study HLX14-001

Part I

All the subjects (24 [100%]) enrolled in part I of the study experienced treatment emergent adverse events (TEAEs), all of which were Grade 1 or 2. A total of 22 (91.7%) subjects experienced treatment-related AEs (TRAEs), including 10 (83.3%) subjects in the HLX14 group and 12 (100%) subjects in the EU-Prolia group.

A total of 22 (91.7%) subjects experienced treatment-related adverse events (TRAEs). The incidences of TRAEs were similar between the HLX14 group and EU-Prolia group. The most common (incidence ≥ 10% in the total subjects) TRAEs by PT were blood cholesterol increased, upper respiratory tract infection, blood calcium decreased, blood phosphorus decreased, blood triglycerides increased, aspartate aminotransferase increased, and neutrophil percentage increased. The incidences and categories of the most common (incidence ≥ 10% in the total subjects) TRAEs were comparable between the two treatment groups.

Table 22. Summary of Treatment-related Adverse Events in Part I of the Study by SOC and PT (Safety Set)

System Organ Class (SOC) Preferred Term (PT)	HLX14 (N=12)	EU-Prolia® (N=12)	Total (N=24)
Subjects with at least one Treatment-related AE, n (%) E	10 (83.3) 39	12 (100) 59	22 (91.7) 98
Investigations, n (%) E	8 (66.7) 30	11 (91.7) 51	19 (79.2) 81
Blood phosphorus decreased	2 (16.7) 5	7 (58.3) 23	9 (37.5) 28
Blood cholesterol increased	4 (33.3) 9	2 (16.7) 5	6 (25.0) 14
Blood calcium decreased	3 (25.0) 6	2 (16.7) 4	5 (20.8) 10
Aspartate aminotransferase increased	1 (8.3) 1	3 (25.0) 3	4 (16.7) 4
Blood triglycerides increased	2 (16.7) 5	2 (16.7) 4	4 (16.7) 9
Neutrophil percentage increased	1 (8.3) 2	2 (16.7) 3	3 (12.5) 5
Alanine aminotransferase increased	0	2 (16.7) 2	2 (8.3) 2
Neutrophil count increased	0	2 (16.7) 4	2 (8.3) 4
Blood bilirubin increased	0	1 (8.3) 1	1 (4.2) 1
Gamma-glutamyltransferase increased	0	1 (8.3) 1	1 (4.2) 1
Neutrophil count decreased	1 (8.3) 1	0	1 (4.2) 1
White blood cell count decreased	1 (8.3) 1	0	1 (4.2) 1
White blood cell count increased	0	1 (8.3) 1	1 (4.2) 1
Infections and infestations, n (%) E	5 (41.7) 6	4 (33.3) 6	9 (37.5) 12
Upper respiratory tract infection	4 (33.3) 5	3 (25.0) 4	7 (29.2) 9
Oral herpes	1 (8.3) 1	1 (8.3) 1	2 (8.3) 2
Tonsillitis	0	1 (8.3) 1	1 (4.2) 1
Musculoskeletal and connective tissue disorders, n (%) E	3 (25.0) 3	2 (16.7) 2	5 (20.8) 5
Pain in extremity	1 (8.3) 1	1 (8.3) 1	2 (8.3) 2
Arthralgia	1 (8.3) 1	0	1 (4.2) 1
Back pain	0	1 (8.3) 1	1 (4.2) 1
Tenosynovitis	1 (8.3) 1	0	1 (4.2) 1

N: The numbers of subjects in the analysis set; n: The numbers of subjects in specific category; %: (n/N*100). E : Events

Part II

All the subjects (228 [100%]) enrolled in part II of the study experienced **TEAEs**. 17 (7.5%) subjects experienced Grade ≥ 3 TEAEs, including 3 (5.2%) subjects in the HLX14 group, 6 (10.5%) subjects in the US-Prolia group, 6 (10.7%) subjects in the EU-Prolia group, and 2 (3.5%) subjects in the CN-Prolia group

A total of 190 (83.3%) subjects experienced **TRAEs**. Seven (3.1%) subjects experienced Grade ≥ 3 TRAEs. The incidences and severities of TRAEs were similar between the HLX14 group, US-Prolia group, EU-Prolia group, and CN-Prolia group. The most common (incidence ≥ 10% in the total subjects) TRAEs by PT were blood phosphorus decreased, blood triglycerides increased, hypophosphataemia, alanine aminotransferase increased, blood cholesterol increased, protein urine present, aspartate aminotransferase increased, and blood calcium decreased. The incidences and categories of the most common (incidence ≥ 10% in the total subjects) TRAEs and Grade ≥ 3 TRAEs were comparable between the HLX14 group, US-Prolia group, EU-Prolia group, and CN-Prolia group.

Table 23. Summary of TREAs in part II of the study by SOC and PT (SS)

System Organ Class Preferred Term	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Total (N=228)
Subjects with at least one Treatment-related AE, n (%) E	48 (82.8) 214	48 (84.2) 182	48 (85.7) 195	46 (80.7) 202	190 (83.3) 793
Investigations, n (%) E	42 (72.4) 160	40 (70.2) 138	46 (82.1) 151	44 (77.2) 153	172 (75.4) 602
Blood phosphorus decreased	12 (20.7) 17	11 (19.3) 23	11 (19.6) 21	14 (24.6) 29	48 (21.1) 90
Alanine aminotransferase increased	10 (17.2) 12	7 (12.3) 11	12 (21.4) 18	9 (15.8) 14	38 (16.7) 55
Blood cholesterol increased	9 (15.5) 15	12 (21.1) 21	8 (14.3) 16	4 (7.0) 9	33 (14.5) 61
Blood triglycerides increased	11 (19.0) 17	6 (10.5) 14	11 (19.6) 17	5 (8.8) 10	33 (14.5) 58
Aspartate aminotransferase increased	7 (12.1) 7	6 (10.5) 7	6 (10.7) 6	9 (15.8) 11	28 (12.3) 31
Protein urine present	9 (15.5) 10	4 (7.0) 4	6 (10.7) 6	8 (14.0) 13	27 (11.8) 33
Blood calcium decreased	3 (5.2) 3	7 (12.3) 13	7 (12.5) 11	8 (14.0) 10	25 (11.0) 37
Neutrophil count increased	8 (13.8) 13	5 (8.8) 6	2 (3.6) 3	6 (10.5) 6	21 (9.2) 28
Neutrophil count decreased	6 (10.3) 13	2 (3.5) 4	6 (10.7) 7	5 (8.8) 5	19 (8.3) 29
Blood uric acid increased	3 (5.2) 5	5 (8.8) 5	7 (12.5) 9	2 (3.5) 4	17 (7.5) 23
White blood cell count decreased	5 (8.6) 8	4 (7.0) 6	3 (5.4) 5	5 (8.8) 5	17 (7.5) 24
Blood creatinine increased	5 (8.6) 8	2 (3.5) 2	3 (5.4) 5	6 (10.5) 8	16 (7.0) 23
Blood calcium increased	5 (8.6) 6	4 (7.0) 4	3 (5.4) 3	1 (1.8) 1	13 (5.7) 14
White blood cell count increased	6 (10.3) 8	2 (3.5) 2	2 (3.6) 4	1 (1.8) 1	11 (4.8) 15
Lymphocyte count decreased	3 (5.2) 4	1 (1.8) 1	4 (7.1) 6	2 (3.5) 2	10 (4.4) 13
Monocyte count increased	3 (5.2) 7	2 (3.5) 2	2 (3.6) 5	3 (5.3) 4	10 (4.4) 18
Gamma-glutamyltransferase increased	1 (1.7) 1	4 (7.0) 7	1 (1.8) 1	2 (3.5) 3	8 (3.5) 12
Glomerular filtration rate decreased	1 (1.7) 1	1 (1.8) 1	1 (1.8) 1	4 (7.0) 4	7 (3.1) 7
Neutrophil percentage increased	1 (1.7) 1	2 (3.5) 3	1 (1.8) 1	3 (5.3) 5	7 (3.1) 10
Blood bilirubin increased	1 (1.7) 2	0	0	4 (7.0) 5	5 (2.2) 7
Lymphocyte count increased	0	1 (1.8) 2	1 (1.8) 3	2 (3.5) 2	4 (1.8) 7
Blood potassium increased	1 (1.7) 2	0	1 (1.8) 1	0	2 (0.9) 3
Blood magnesium decreased	0	0	1 (1.8) 1	0	1 (0.4) 1
Eosinophil count increased	0	0	1 (1.8) 1	0	1 (0.4) 1
Eosinophil percentage increased	0	0	0	1 (1.8) 2	1 (0.4) 2
Metabolism and nutrition disorders, n (%) E	14 (24.1) 31	16 (28.1) 27	12 (21.4) 19	17 (29.8) 36	59 (25.9) 113
Hypophosphataemia	11 (19.0) 20	10 (17.5) 16	4 (7.1) 8	12 (21.1) 24	37 (16.2) 68
Hypokalaemia	4 (6.9) 6	3 (5.3) 4	3 (5.4) 4	4 (7.0) 4	14 (6.1) 18
Hyperkalaemia	1 (1.7) 1	1 (1.8) 2	1 (1.8) 1	2 (3.5) 3	5 (2.2) 7
Hypocalcaemia	1 (1.7) 1	1 (1.8) 1	2 (3.6) 2	1 (1.8) 1	5 (2.2) 5
Hyperuricaemia	1 (1.7) 1	1 (1.8) 1	1 (1.8) 1	1 (1.8) 1	4 (1.8) 4

System Organ Class Preferred Term	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Total (N=228)
Hypertriglyceridaemia	0	1 (1.8) 2	1 (1.8) 1	1 (1.8) 1	3 (1.3) 4
Hypomagnesaemia	0	1 (1.8) 1	2 (3.6) 2	0	3 (1.3) 3
Hypoglycaemia	2 (3.4) 2	0	0	0	2 (0.9) 2
Hyponatraemia	0	0	0	1 (1.8) 2	1 (0.4) 2
Musculoskeletal and connective tissue disorders, n (%) E	6 (10.3) 6	5 (8.8) 6	10 (17.9) 15	0	21 (9.2) 27
Arthralgia	4 (6.9) 4	4 (7.0) 4	7 (12.5) 7	0	15 (6.6) 15
Back pain	1 (1.7) 1	0	3 (5.4) 3	0	4 (1.8) 4
Muscle spasms	0	1 (1.8) 1	1 (1.8) 1	0	2 (0.9) 2
Myalgia	0	0	2 (3.6) 2	0	2 (0.9) 2
Arthropathy	0	0	1 (1.8) 1	0	1 (0.4) 1
Pain in extremity	0	0	1 (1.8) 1	0	1 (0.4) 1
Periarthritis	1 (1.7) 1	0	0	0	1 (0.4) 1
Synovitis	0	1 (1.8) 1	0	0	1 (0.4) 1
Cardiac disorders, n (%) E	5 (8.6) 6	2 (3.5) 4	0	3 (5.3) 3	10 (4.4) 13
Atrioventricular block first degree	3 (5.2) 3	1 (1.8) 1	0	2 (3.5) 2	6 (2.6) 6
Ventricular extrasystoles	2 (3.4) 3	1 (1.8) 3	0	0	3 (1.3) 6
Supraventricular extrasystoles	0	0	0	1 (1.8) 1	1 (0.4) 1
Infections and infestations, n (%) E	4 (6.9) 7	2 (3.5) 2	2 (3.6) 2	1 (1.8) 2	9 (3.9) 13
Gingivitis	2 (3.4) 2	0	0	0	2 (0.9) 2
Pericoronitis	1 (1.7) 2	0	1 (1.8) 1	0	2 (0.9) 3
Periodontitis	1 (1.7) 1	0	0	1 (1.8) 1	2 (0.9) 2
Upper respiratory tract infection	0	1 (1.8) 1	1 (1.8) 1	0	2 (0.9) 2
Arthritis infective	0	1 (1.8) 1	0	0	1 (0.4) 1
Eczema infected	0	0	0	1 (1.8) 1	1 (0.4) 1
Oral herpes	1 (1.7) 1	0	0	0	1 (0.4) 1
Tooth abscess	1 (1.7) 1	0	0	0	1 (0.4) 1
Blood and lymphatic system disorders, n (%) E	2 (3.4) 4	1 (1.8) 2	2 (3.6) 5	1 (1.8) 1	6 (2.6) 12
Neutropenia	0	1 (1.8) 2	1 (1.8) 4	1 (1.8) 1	3 (1.3) 7
Anaemia	1 (1.7) 2	0	0	0	1 (0.4) 2
Eosinophilia	1 (1.7) 2	0	0	0	1 (0.4) 2
Leukopenia	0	0	1 (1.8) 1	0	1 (0.4) 1
Skin and subcutaneous tissue disorders, n (%) E	0	0	0	4 (7.0) 7	4 (1.8) 7
Rash	0	0	0	2 (3.5) 5	2 (0.9) 5
Eczema	0	0	0	1 (1.8) 1	1 (0.4) 1
Urticaria papular	0	0	0	1 (1.8) 1	1 (0.4) 1
Gastrointestinal disorders, n (%) E	0	0	2 (3.6) 2	0	2 (0.9) 2

Mouth ulceration	0	0	2 (3.6) 2	0	2 (0.9) 2
General disorders and administration site conditions, n (%) E	0	1 (1.8) 1	1 (1.8) 1	0	2 (0.9) 2
Influenza like illness	0	0	1 (1.8) 1	0	1 (0.4) 1
Injection site reaction	0	1 (1.8) 1	0	0	1 (0.4) 1
Ear and labyrinth disorders, n (%) E	0	1 (1.8) 2	0	0	1 (0.4) 2
Hypoacusis	0	1 (1.8) 1	0	0	1 (0.4) 1
Tinnitus	0	1 (1.8) 1	0	0	1 (0.4) 1

N: The numbers of subjects in the analysis set; n: The numbers of subjects in specific category; %: (n/N*100). E : Events
TEAE was defined as AEs from the start of the study drugs to the end of the study, and any study treatment-related SAE after the end of the study.
All AE terms were coded by MedDRA Version 26.1.

Adverse Events by Severity

No subjects experienced **Grade ≥ 3 TEAEs or TRAEs** in part I of the study.

A total of 17 (7.5%) subjects enrolled in part II of the study experienced **Grade ≥ 3 TEAEs**.

In the HLX14 group, 3 (5.2%) subjects experienced Grade ≥ 3 TEAEs. The reported PT were blood triglycerides increased (2 subjects, 3.4%) and blood potassium increased (1 subject, 1.7%).

In the US-Prolia group, 6 (10.5%) subjects experienced Grade ≥ 3 TEAEs. The reported PT were blood triglycerides increased (2 subjects, 3.5%), blood calcium increased (1 subject, 1.8%), neutropenia (1 subject, 1.8%), arthritis infective (1 subject, 1.8%), and synovitis (1 subject, 1.8%). In the EU-Prolia group, 6 (10.7%) subjects experienced Grade ≥ 3 TEAEs. The reported PT were blood triglycerides increased (3 subjects, 5.4%), neutrophil count decreased (2 subjects, 3.6%), blood calcium increased (1 subject, 1.8%), and blood magnesium increased (1 subject, 1.8%). In the CN-Prolia group, 2 (3.5%) subjects experienced Grade ≥ 3 TEAEs. The reported PT were blood triglycerides increased (2 subjects, 3.5%).

Table 24. Summary of treatment-related AEs with grade ≥3 in part II of the study SOC and PT (SS)

System Organ Class (SOC) Preferred Term (PT)	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Total (N=228)
Subjects with at least one Grade ≥ 3 Treatment-related AE, n (%) E	2 (3.4) 2	4 (7.0) 4	1 (1.8) 1	0	7 (3.1) 7
Investigations, n (%) E	2 (3.4) 2	1 (1.8) 1	1 (1.8) 1	0	4 (1.8) 4
Blood triglycerides increased	1 (1.7) 1	1 (1.8) 1	1 (1.8) 1	0	3 (1.3) 3
Blood potassium increased	1 (1.7) 1	0	0	0	1 (0.4) 1
Blood and lymphatic system disorders, n (%) E	0	1 (1.8) 1	0	0	1 (0.4) 1
Neutropenia	0	1 (1.8) 1	0	0	1 (0.4) 1
Infections and infestations, n (%) E	0	1 (1.8) 1	0	0	1 (0.4) 1
Arthritis infective	0	1 (1.8) 1	0	0	1 (0.4) 1
Musculoskeletal and connective tissue disorders, n (%) E	0	1 (1.8) 1	0	0	1 (0.4) 1
Synovitis	0	1 (1.8) 1	0	0	1 (0.4) 1

TEAE was defined as AEs from the start of the study drugs to the end of the study, and any study treatment-related SAE after the end of the study.
All AE terms were coded by MedDRA Version 26.1.
Data source: Module 5.3.3.1 HLX14-001 CSR, Table 34.

Study HLX14-002-PMOP301

In the SS of study HLX14-002-PMOP301 448 (87.2%) subjects experienced **TEAEs**, including 222 (86.7%) subjects in the HLX14 group and 226 (87.6%) in the Prolia group. The most common TEAEs (incidence ≥10% in the total subjects) by PT were pyrexia (HLX14 group vs. Prolia group: 19.5% vs. 22.5%), cough (19.1% vs. 20.5%), hyperlipidaemia (15.2% vs. 17.4%), vitamin D deficiency (12.9% vs. 16.3%), and urinary tract infection (12.5% vs. 14.7%).

In the SS, a total of 147 (28.6%) subjects experienced **TRAEs**, including 67 (26.2%) subjects in the HLX14 group and 80 (31.0%) subjects in the Prolia group. The most common TRAEs (incidence ≥ 1% in the total subjects) by PT were vitamin D deficiency (HLX14 group vs. Prolia group: 3.5% vs. 4.3%), hyperlipidaemia (3.5% vs. 3.9%), hypercalcaemia (2.7% vs. 4.7%), urinary tract infection (2.3% vs. 5.0%), hypocalcaemia (2.3% vs. 4.3%), arthralgia (2.3% vs. 0.4%), and constipation (1.2% vs. 1.6%).

A total of 116 (22.6%) subjects experienced HLX14/Prolia-related AEs, including 52 (20.3%) subjects in the HLX14 group and 64 (24.8%) subjects in the Prolia group. The most common HLX14/Prolia-related AEs (incidence ≥ 1% in the total subjects) by PT were hyperlipidaemia (HLX14 group vs. Prolia group: 3.5% vs. 3.9%), hypocalcaemia (2.3% vs. 4.3%), urinary tract infection (2.3% vs. 5.0%), arthralgia (2.3% vs. 0.4%), and vitamin D deficiency (2.0% vs. 1.9%).

Safety data from study HLX14-002-PMOP301 beyond the first year are presented in a separate section below (3.3.7.10.)

Table 25. Summary of HLX14/Prolia-related Adverse Events by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects with at least one HLX14/Prolia-related AE, n (%) E [1]	52 (20.3) 98	64 (24.8) 92	116 (22.6) 190
Metabolism and nutrition disorders, n (%) E	26 (10.2) 29	29 (11.2) 35	55 (10.7) 64
Hyperlipidaemia	9 (3.5) 10	10 (3.9) 10	19 (3.7) 20
Hypocalcaemia	6 (2.3) 6	11 (4.3) 12	17 (3.3) 18
Vitamin D deficiency	5 (2.0) 6	5 (1.9) 5	10 (1.9) 11
Hypophosphataemia	3 (1.2) 3	1 (0.4) 1	4 (0.8) 4
Hypertriglyceridaemia	2 (0.8) 2	1 (0.4) 1	3 (0.6) 3
Hypercalcaemia	0	2 (0.8) 2	2 (0.4) 2
Diabetes mellitus	0	1 (0.4) 1	1 (0.2) 1
Hypercholesterolaemia	0	1 (0.4) 2	1 (0.2) 2
Hyperphosphataemia	1 (0.4) 1	0	1 (0.2) 1
Hyperuricaemia	0	1 (0.4) 1	1 (0.2) 1
Hypokalaemia	1 (0.4) 1	0	1 (0.2) 1
Investigations, n (%) E	12 (4.7) 20	12 (4.7) 14	24 (4.7) 34
Blood alkaline phosphatase decreased	2 (0.8) 2	1 (0.4) 1	3 (0.6) 3

Blood glucose increased	2 (0.8) 2	1 (0.4) 1	3 (0.6) 3
Blood phosphorus decreased	2 (0.8) 2	1 (0.4) 1	3 (0.6) 3
Urinary occult blood positive	1 (0.4) 1	2 (0.8) 2	3 (0.6) 3
Alanine aminotransferase increased	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Gamma-glutamyltransferase increased	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Glutathione reductase activity increased	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Neutrophil count decreased	0	2 (0.8) 2	2 (0.4) 2
Aspartate aminotransferase increased	1 (0.4) 1	0	1 (0.2) 1
Blood bilirubin increased	0	1 (0.4) 1	1 (0.2) 1
Blood cholesterol increased	0	1 (0.4) 1	1 (0.2) 1
Blood cholinesterase increased	1 (0.4) 1	0	1 (0.2) 1
Blood creatine phosphokinase increased	0	1 (0.4) 1	1 (0.2) 1
Electrocardiogram Q wave abnormal	1 (0.4) 1	0	1 (0.2) 1
Electrocardiogram ST segment abnormal	1 (0.4) 1	0	1 (0.2) 1
Electrocardiogram T wave abnormal	1 (0.4) 1	0	1 (0.2) 1
Glycocholic acid increased	1 (0.4) 1	0	1 (0.2) 1
Haemoglobin increased	1 (0.4) 1	0	1 (0.2) 1
Red blood cell count increased	1 (0.4) 1	0	1 (0.2) 1
Vitamin D decreased	0	1 (0.4) 1	1 (0.2) 1
White blood cell count decreased	1 (0.4) 1	0	1 (0.2) 1
White blood cells urine positive	1 (0.4) 1	0	1 (0.2) 1
Infections and infestations, n (%) E	8 (3.1) 10	13 (5.0) 17	21 (4.1) 27
Urinary tract infection	6 (2.3) 8	13 (5.0) 17	19 (3.7) 25
Bacteriuria	1 (0.4) 1	0	1 (0.2) 1
Pulpitis dental	1 (0.4) 1	0	1 (0.2) 1
Musculoskeletal and connective tissue disorders, n (%) E	10 (3.9) 13	5 (1.9) 7	15 (2.9) 20
Arthralgia	6 (2.3) 6	1 (0.4) 2	7 (1.4) 8
Back pain	2 (0.8) 2	1 (0.4) 2	3 (0.6) 4
Muscle spasms	1 (0.4) 2	1 (0.4) 1	2 (0.4) 3
Pain in extremity	0	2 (0.8) 2	2 (0.4) 2
Arthropathy	1 (0.4) 1	0	1 (0.2) 1
Bone pain	1 (0.4) 1	0	1 (0.2) 1
Myalgia	1 (0.4) 1	0	1 (0.2) 1
Gastrointestinal disorders, n (%) E	6 (2.3) 9	5 (1.9) 6	11 (2.1) 15
Constipation	1 (0.4) 1	2 (0.8) 3	3 (0.6) 4
Nausea	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Abdominal pain	1 (0.4) 4	0	1 (0.2) 4
Colitis	1 (0.4) 1	0	1 (0.2) 1
Dry mouth	1 (0.4) 1	0	1 (0.2) 1
Gastrooesophageal reflux disease	0	1 (0.4) 1	1 (0.2) 1
Mouth ulceration	1 (0.4) 1	0	1 (0.2) 1
Toothache	0	1 (0.4) 1	1 (0.2) 1
Cardiac disorders, n (%) E	5 (2.0) 7	2 (0.8) 2	7 (1.4) 9
Myocardial ischaemia	2 (0.8) 4	1 (0.4) 1	3 (0.6) 5
Angina pectoris	1 (0.4) 1	0	1 (0.2) 1
Bundle branch block right	0	1(0.4) 1	1 (0.2) 1
Palpitations	1 (0.4) 1	0	1 (0.2) 1
Sinus bradycardia	1 (0.4) 1	0	1 (0.2) 1
Skin and subcutaneous tissue disorders, n (%) E	0	5 (1.9) 5	5 (1.0) 5
Erythema	0	2 (0.8) 2	2 (0.4) 2
Dermatitis	0	1 (0.4) 1	1 (0.2) 1
Dermatitis allergic	0	1 (0.4) 1	1 (0.2) 1

Pruritus	0	1 (0.4) 1	1 (0.2) 1
Blood and lymphatic system disorders, n (%) E	2 (0.8) 3	2 (0.8) 3	4 (0.8) 6
Anaemia	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Leukopenia	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Neutropenia	0	1 (0.4) 1	1 (0.2) 1
Thrombocytopenia	1 (0.4) 1	0	1 (0.2) 1
Renal and urinary disorders, n (%) E	2 (0.8) 2	1 (0.4) 1	3 (0.6) 3
Haematuria	1 (0.4) 1	0	1 (0.2) 1
Pollakiuria	1 (0.4) 1	0	1 (0.2) 1
Renal failure	0	1 (0.4) 1	1 (0.2) 1
General disorders and administration site conditions, n (%) E	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Fatigue	0	1 (0.4) 1	1 (0.2) 1
Injection site pruritus	1 (0.4) 1	0	1 (0.2) 1
Vascular disorders, n (%) E	2 (0.8) 2	0	2 (0.4) 2
Hot flush	1 (0.4) 1	0	1 (0.2) 1
Hypertension	1 (0.4) 1	0	1 (0.2) 1
Hepatobiliary disorders, n (%) E	1 (0.4) 1	0	1 (0.2) 1
Hepatic function abnormal	1 (0.4) 1	0	1 (0.2) 1
Nervous system disorders, n (%) E	1 (0.4) 1	0	1 (0.2) 1
Dizziness	1 (0.4) 1	0	1 (0.2) 1
Respiratory, thoracic and mediastinal disorders, n (%) E	0	1(0.4)1	1(0.2) 1
Rhinitis allergic	0	1(0.4)1	1 (0.2) 1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
E: Events.
AE: Adverse Event; TEAE: Treatment-Emergent Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events.
[1] TEAE was defined as an AE that first occurred or worsened in severity in the period from the first dose administrated date to Week 52 or to the end for the subjects who ended the study before Week 52.
System Organ Class and Preferred Term were coded using MedDRA version 26.1.

Adverse Events by Severity

A total of 43 (8.4%) subjects experienced **Grade ≥ 3 TEAEs**, including 24 (9.4%) subjects in the HLX14 group and 19 (7.4%) subjects in the Prolia group. The most common Grade ≥ 3 TEAEs (occurred in at least 2 subjects, in the total subjects) by PT were humerus fracture (HLX14 group vs. Prolia group: 0.8%vs. 0), appendicitis (0.4% vs. 0.4%), transient ischaemic attack (0.4% vs. 0.4%), rotator cuff syndrome (0.4% vs. 0.4%), cerebral infarction (0.4% vs. 0.4%), coronary artery disease (0.4% vs. 0.4%), and haemorrhoids (0 vs 0.8%).

In SS, 3 (0.6%) subjects experienced **Grade ≥ 3 TRAEs**, including 2 (0.8%) subjects in the HLX14 group and 1 (0.4%) subject in the Prolia group. The Grade ≥ 3 TRAEs by PT were hyperlipidaemia (HLX14 group vs. Prolia group: 0.4% vs. 0), ureterolithiasis (0.4% vs. 0), and synovitis (0 vs. 0.4%). Only 1 (0.4%) subject in the HLX14 group experienced a Grade ≥ 3 HLX14-related AE, and the PT was hyperlipidaemia.

Table 26. Summary of HLX14/Prolia-related Adverse Events with CTCAE Grade ≥ 3 by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects with at least one HLX14/Prolia-related AE grade ≥ 3, n (%) E [1]	1 (0.4) 1	0	1 (0.2) 1
Metabolism and nutrition disorders, n (%) E	1 (0.4) 1	0	1 (0.2) 1
Hyperlipidaemia	1 (0.4) 1	0	1 (0.2) 1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
E: Events.
AE: Adverse Event; TEAE: Treatment-Emergent Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events
[1] TEAE was defined as an AE that first occurred or worsened in severity in the period from the first dose administrated date to Week 52 or to the end for the subjects who ended the study before Week 52.
System Organ Class and Preferred Term were coded using MedDRA version 26.1.

2.5.8.3. Serious adverse event/deaths/other significant events

Adverse events of special interest (AESI) are scientifically and medically concerned events for study drug that may require close monitoring and prompt communication between the Sponsor and the investigator. Timely reporting of AESI allows continuous monitoring of these events for understand their association with the use of the investigational product. An AESI that meets SAE criteria should be rapidly reported following the relevant procedures of SAE reporting.

The AESIs in this study include: Hypersensitivity reactions, hypocalcemia, serious infections (including skin infection), osteonecrosis of the jaw, atypical femur fracture, etc. The occurrence of an AESI should be recorded on the AE page by the investigator.

- Hypersensitivity reactions: Clinically significant hypersensitivity reactions related to denosumab that have been reported, including anaphylaxis. The symptoms include: Hypotension, dyspnoea, throat tightness, facial and upper respiratory edema, itching and urticaria. In the event of any anaphylaxis or any other clinically significant anaphylactic symptoms, appropriate treatment should be given.
- Hypocalcemia: Hypocalcemia may be further exacerbated following the administration of denosumab. Calcium and mineral (phosphorus and magnesium) levels will be monitored clinically within 14 days following subcutaneous injection of investigational product. Postmarketing surveillance suggests hypocalcaemia may last for weeks or months. Close monitoring and intravenous and/or oral calcium supplements are necessary, with or without vitamin D supplements.
- Serious infections: In a clinical trial enrolling more than 7,800 postmenopausal women with osteoporosis, more serious infections requiring hospitalization occurred in Prolia group compared with placebo group, such as more serious skin infections, abdominal infections, urinary tract infections, and ear infections, and endocarditis. The incidence of opportunistic infection in placebo group is similar to that in Prolia group, and the overall incidence of infections is also similar between the two treatment groups. The recommendation of prompt medical management is given to subjects in the event of any symptom or sign of serious infections (including cellulitis).
- Osteonecrosis of the jaw (ONJ): Osteonecrosis of the jaw (ONJ) is generally associated with tooth extraction and/or local infection with delayed healing, which may occur simultaneously. ONJ has been reported by patients treated with denosumab. Prior to the initiation of denosumab treatment, patients are required to have examination by the prescriber. For patients with risk factors for developing ONJ, dental examination with appropriate precautions

is recommended prior to the initiation of denosumab treatment. Risk factors contributing to ONJ include invasive dental procedures (e.g., tooth extraction, tooth implantation and oral surgery), malignancies, concomitant treatments (e.g., chemotherapy and antiangiogenic agent), poor oral hygiene, concomitant diseases (e.g., periodontal and/or other pre-existing dental disorders, anemia, coagulation disorders and infections). Patients who are suspected to be experiencing or have experienced ONJ during treatment should be treated by the dentist or/and dental surgeon. However, extensive dental surgery for the treatment of ONJ may also lead to exacerbation. For patients undergoing invasive dental procedures, the treating physician and/or oral surgeon should guide each patient's management plan based on his/her benefit/risk assessment.

- Atypical femur fracture: Atypical femur fracture has been reported in patients treated with Prolia. However, the casual relationship to drug could not be determined, because such fracture has also occurred in patients with osteoporosis who have not received anti-bone resorption medications. During the trial, subjects are recommended to report new or abnormal pain in thigh, hip or groin. Any subject with pain in thigh or groin should be suspected of having atypical fracture and should be assessed to rule out incomplete fracture of femur.

Adverse events of special interest

Study HLX14-001

Table 27. Summary of treatment-related AESIs in Part I of the Study by SOC and PT (SS)

System Organ Class (SOC) Preferred Term (PT)	HLX14 (N=12)		EU-Prolia® (N=12)		Total (N=24)	
Subjects with at least one Treatment-related AESI, n (%) E	3 (25.0)	6	2 (16.7)	4	5 (20.8)	10
Investigations, n (%) E	3 (25.0)	6	2 (16.7)	4	5 (20.8)	10
Blood calcium decreased	3 (25.0)	6	2 (16.7)	4	5 (20.8)	10

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100). E: Events.
TEAE is defined as adverse events from the start of the study drugs to the end of the study, and any study treatment-related SAE after the end of the study.
AESIs in this study included: hypersensitivity reactions, hypocalcemia, serious infections (including skin infections), osteonecrosis of the jaw and atypical femoral fracture.
All AE terms are coded by MedDRA(Version 26.1).
Source:Listing 16.2.7.6-Part1

Table 28. Summary of treatment-related AESIs in Part II of the Study by SOC and PT (SS)

System Organ Class (SOC) Preferred Term (PT)	HLX14 (N=58)		US-Prolia® (N=57)		EU-Prolia® (N=56)		CN-Prolia® (N=57)		Total (N=228)	
Subjects with at least one Treatment-related AESI, n (%) E	4 (6.9)	4	9 (15.8)	15	9 (16.1)	13	9 (15.8)	11	31 (13.6)	43
Investigations, n (%) E	3 (5.2)	3	7 (12.3)	13	7 (12.5)	11	8 (14.0)	10	25 (11.0)	37
Blood calcium decreased	3 (5.2)	3	7 (12.3)	13	7 (12.5)	11	8 (14.0)	10	25 (11.0)	37
Metabolism and nutrition disorders, n (%) E	1 (1.7)	1	1 (1.8)	1	2 (3.6)	2	1 (1.8)	1	5 (2.2)	5
Hypocalcaemia	1 (1.7)	1	1 (1.8)	1	2 (3.6)	2	1 (1.8)	1	5 (2.2)	5
Infections and infestations, n (%) E	0		1 (1.8)	1	0		0		1 (0.4)	1
Arthritis infective	0		1 (1.8)	1	0		0		1 (0.4)	1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100). E: Events.
TEAE is defined as adverse events from the start of the study drugs to the end of the study, and any study treatment-related SAE after the end of the study.
AESIs in this study included: hypersensitivity reactions, hypocalcemia, serious infections (including skin infections), osteonecrosis of the jaw and atypical femoral fracture.
All AE terms are coded by MedDRA(Version 26.1).
Source:Listing 16.2.7.6

Study HLX14-002-PMOP301

Table 29. Summary of AESIs by System Organ Class and Preferred Term (SS)

System Organ Class Preferred Term	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects with at least one AESI, n (%) E [1]	10 (3.9) 12	16 (6.2) 18	26 (5.1) 30
Metabolism and nutrition disorders, n (%) E	7 (2.7) 8	13 (5.0) 14	20 (3.9) 22
Hypocalcaemia	7 (2.7) 8	13 (5.0) 14	20 (3.9) 22
Infections and infestations, n (%) E	4 (1.6) 4	2 (0.8) 3	6 (1.2) 7
Appendicitis	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Complicated appendicitis	1 (0.4) 1	0	1 (0.2) 1
Gastroenteritis	1 (0.4) 1	0	1 (0.2) 1
Pneumonia	0	1 (0.4) 1	1 (0.2) 1
Septic shock	0	1 (0.4) 1	1 (0.2) 1
Urinary tract infection	1 (0.4) 1	0	1 (0.2) 1
Skin and subcutaneous tissue disorders, n (%) E	0	1 (0.4) 1	1 (0.2)1
Dermatitis allergic	0	1 (0.4) 1	1 (0.2) 1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
E: Events.
AE: Adverse Event; TEAE: Treatment-Emergent Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events
[1] TEAE was defined as an AE that first occurred or worsened in severity in the period from the first dose administrated date to Week 52 or to the end for the subjects who ended the study before Week 52.
System Organ Class and Preferred Term were coded using MedDRA version 26.1.
AESIs in this study included: hypersensitivity reactions, hypocalcemia, serious infections (including skin infections), osteonecrosis of the jaw and atypical femoral fracture.

Table 30. Summary of HLX14/Prolia-related AESIs by System Organ Class and Preferred Term (SS)

System Organ Class Preferred Term	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects with at least one HLX14/Prolia-related AESI, n (%) E [1]	6 (2.3) 6	12 (4.7) 13	18 (3.5) 19
Metabolism and nutrition disorders, n (%) E	6 (2.3) 6	11 (4.3) 12	17 (3.3) 18
Hypocalcaemia	6 (2.3) 6	11 (4.3) 12	17 (3.3) 18
Skin and subcutaneous tissue disorders, n (%) E	0	1 (0.4) 1	1 (0.2) 1
Dermatitis allergic	0	1 (0.4) 1	1 (0.2) 1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
E: Events.
AE: Adverse Event; TEAE: Treatment-Emergent Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events.
[1] TEAE was defined as an AE that first occurred or worsened in severity in the period from the first dose administrated date to Week 52 or to the end for the subjects who ended the study before Week 52.
System Organ Class and Preferred Term were coded using MedDRA version 26.1.

Serious adverse events

Study HLX14-001

Part I: No SAEs were reported

Part II:

Table 31. Summary of treatment-related SAEs in Part II of the Study by SOC and PT (SS)

System Organ Class (SOC) Preferred Term (PT)	HLX14 (N=58)	US-Prolia® (N=57)		EU-Prolia® (N=56)	CN-Prolia® (N=57)	Total (N=228)	
Subjects with at least one SAE, n (%) E	0	2 (3.5)	2	0	0	2 (0.9)	2
Infections and infestations, n (%) E	0	1 (1.8)	1	0	0	1 (0.4)	1
Arthritis infective	0	1 (1.8)	1	0	0	1 (0.4)	1
Musculoskeletal and connective tissue disorders, n (%) E	0	1 (1.8)	1	0	0	1 (0.4)	1
Synovitis	0	1 (1.8)	1	0	0	1 (0.4)	1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100). E: Events.
TEAE is defined as adverse events from the start of the study drugs to the end of the study, and any study treatment-related SAE after the end of the study.
All AE terms are coded by MedDRA(Version 26.1).
Source:Listing 16.2.7.7
[Source: t adae freq.sas] 18JAN2024T18:27:03 EDC DATE: 18JAN2024T13:47:49

Study HLX14-002-PMOP301

Table 32. Summary of Treatment Emergent Serious Adverse Events by SOC and PT (SS)

System Organ Class Preferred Term	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects with at least one serious TEAE, n (%) E [1]	22 (8.6) 24	16 (6.2) 19	38 (7.4) 43
Injury, poisoning and procedural complications, n (%) E	6 (2.3) 6	4 (1.6) 4	10 (1.9) 10
Humerus fracture	2 (0.8) 2	0	2 (0.4) 2
Concussion	1 (0.4) 1	0	1 (0.2) 1
Femoral neck fracture	1 (0.4) 1	0	1 (0.2) 1
Lumbar vertebral fracture	0	1 (0.4) 1	1 (0.2) 1
Meniscus injury	1 (0.4) 1	0	1 (0.2) 1
Patella fracture	0	1 (0.4) 1	1 (0.2) 1
Spinal compression fracture	0	1 (0.4) 1	1 (0.2) 1
Thoracic vertebral fracture	1 (0.4) 1	0	1 (0.2) 1
Toxicity to various agents	0	1 (0.4) 1	1 (0.2) 1
Musculoskeletal and connective tissue disorders, n (%) E	3 (1.2) 3	3 (1.2) 3	6 (1.2) 6
Rotator cuff syndrome	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Intervertebral disc protrusion	0	1 (0.4) 1	1 (0.2) 1
Lumbar spinal stenosis	1 (0.4) 1	0	1 (0.2) 1
Spinal osteoarthritis	1 (0.4) 1	0	1 (0.2) 1
Synovitis	0	1 (0.4) 1	1 (0.2) 1
Gastrointestinal disorders, n (%) E	2 (0.8) 2	3 (1.2) 3	5 (1.0) 5
Haemorrhoids	0	2 (0.8) 2	2 (0.4) 2
Colitis	1 (0.4) 1	0	1 (0.2) 1
Gastritis	0	1 (0.4) 1	1 (0.2) 1
Large intestine polyp	1 (0.4) 1	0	1 (0.2) 1
Infections and infestations, n (%) E	3 (1.2) 3	2 (0.8) 3	5 (1.0) 6
Appendicitis	1 (0.4)1	1 (0.4) 1	2 (0.4) 2
Complicated appendicitis	1 (0.4) 1	0	1 (0.2) 1
Gastroenteritis	1 (0.4) 1	0	1 (0.2) 1
Pneumonia	0	1 (0.4) 1	1 (0.2) 1
Septic shock	0	1 (0.4) 1	1 (0.2) 1
Nervous system disorders, n (%) E	3 (1.2) 4	2 (0.8) 2	5 (1.0) 6
Cerebral infarction	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Transient ischaemic attack	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Intracranial aneurysm	1 (0.4) 1	0	1 (0.2) 1
Lacunar infarction	1 (0.4) 1	0	1 (0.2) 1
Ear and labyrinth disorders, n (%) E	2 (0.8) 2	1 (0.4) 1	3 (0.6)3
Meniere's disease	1 (0.4) 1	0	1 (0.2)1
Otolithiasis	0	1 (0.4) 1	1 (0.2)1
Vertigo positional	1 (0.4) 1	0	1 (0.2)1
Cardiac disorders, n (%) E	1 (0.4) 1	1 (0.4) 1	2 (0.4)2
Coronary artery disease	1 (0.4) 1	1 (0.4) 1	2 (0.4)2
Eye disorders, n (%) E	2 (0.8) 2	0	2 (0.4)2
Cataract	1 (0.4) 1	0	1 (0.2)1
Neovascular age-related macular degeneration	1 (0.4) 1	0	1 (0.2)1
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%) E	0	1 (0.4) 1	1 (0.2)1
Cervix carcinoma	0	1 (0.4) 1	1 (0.2) 1
Renal and urinary disorders, n (%) E	1 (0.4) 1	0	1 (0.2) 1
Ureterolithiasis	1 (0.4) 1	0	1 (0.2)1
Reproductive system and breast disorders, n (%) E	0	1 (0.4) 1	1 (0.2) 1
Uterine polyp	0	1 (0.4) 1	1 (0.2) 1

N: The numbers of subjects in the analysis set; n: The numbers of subjects in specific category; %: (n/N*100). E: Events.
AE: Adverse Event; TEAE: Treatment Emergent Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events.
[1] TEAE was defined as an AE that first occurs or worsens in severity in the period from the first dose administrated date to Week 52 or to the end for the subjects who end the study before Week 52.
System Organ Class and Preferred Term were coded using MedDRA version 26.1.

Table 33. Summary of HLX14/Prolia-related Treatment Emergent Serious Adverse Events by SOC and PT (SS)

System Organ Class Preferred Term	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects with at least one HLX14/Prolia-related serious AE, n (%) E [1]	1 (0.4) 1	0	1 (0.2) 1
Gastrointestinal disorders, n (%) E	1 (0.4) 1	0	1 (0.2) 1
Colitis	1 (0.4) 1	0	1 (0.2) 1

N: The numbers of subjects in the analysis set; n: The numbers of subjects in specific category; %: (n/N*100).
E: Events.
AE: Adverse Event; TEAE: Treatment Emergent Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events.
[1] TEAE was defined as an AE that first occurs or worsens in severity in the period from the first dose administrated date to Week 52 or to the end for the subjects who end the study before Week 52.
System Organ Class and Preferred Term were coded using MedDRA version 26.1.

Deaths

No subjects died during Study HLX14-001 or Study HLX14-002-PMOP301.

Injection site reactions

Study HLX14-001

Part I: No injection site reactions were reported

Part II:

Table 34. Summary of Injection Site Reaction in Part II of the Study by SOC and PT (SS)

System Organ Class (SOC) Preferred Term (PT)	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Total (N=228)
Any injection site reaction, n (%) E	0	1 (1.8) 1	0	0	1 (0.4) 1
General disorders and administration site conditions, n (%) E	0	1 (1.8) 1	0	0	1 (0.4) 1
Injection site reaction	0	1 (1.8) 1	0	0	1 (0.4) 1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100);
E: Events.
TEAE was defined as adverse events from the start of the study drugs to the end of the study, and any study treatment-related SAE after the end of the study.
All AE terms were coded by MedDRA Version 26.1.
Data source: Module 5.3.3.1 HLX14-001 CSR, Table 39.

Study HLX14-002-PMOP301

Table 35. Summary of Injection Site Reactions of Study HLX14-002-PMOP301 by SOC and PT (SS)

System Organ Class Preferred Term	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Subjects with at least one injection site reaction, n (%) E [1]	1 (0.4) 1	2 (0.8) 2	3 (0.6) 3
Skin and subcutaneous tissue disorders, n (%) E	0	2 (0.8) 1	2 (0.4) 2
Erythema	0	2 (0.8) 1	2 (0.4) 2
General disorders and administration site conditions, n (%) E	1 (0.4) 1	0	1 (0.2) 1
Injection site pruritus	1 (0.4) 1	0	1 (0.2) 1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
E: Events.
AE: Adverse Event; TEAE: Treatment Emergent Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events
[1] TEAE was defined as an AE that first occurs or worsens in severity in the period from the first dose administrated date to Week 52 or to the end for the subjects who end the study before Week 52.
System Organ Class and Preferred Term were coded using MedDRA version 26.1.
Data source: Module 5.3.5.1 HLX14-002-PMOP301 CSR, Table 12-9.

2.5.8.4. Laboratory findings

Study HLX14-001

Part I

The most common (incidence ≥ 5% in the total subjects) TEAEs in hematology variables were neutrophil percentage increased (HLX14 group vs. EU-Prolia group: 8.3% vs. 25.0%), lymphocyte count decreased (8.3% vs. 8.3%), neutrophil count increased (0 vs. 25.0%), and white blood cell count increased (0 vs. 16.7%).

The most common (incidence ≥ 5% in the total subjects) TEAEs in serum chemistry variables were blood cholesterol increased (HLX14 group vs. EU-Prolia group: 41.7% vs. 16.7%), blood phosphorus decreased (25.0% vs. 58.3%), blood calcium decreased (25.0% vs. 16.7%), aspartate aminotransferase increased (16.7% vs. 25.0%), blood triglycerides increased (16.7% vs. 16.7%), blood calcium increased (16.7% vs. 8.3%), blood uric acid increased (8.3% vs. 8.3%), and alanine aminotransferase increased (0 vs. 25.0%).

The most common (incidence ≥ 5% in the total subjects) TEAEs in urinalysis variables were urinary occult blood positive (HLX14 group vs. EU-Prolia group: 8.3% vs. 16.7%), and white blood cells urine positive (8.3% vs. 8.3%).

Part II

The most common (incidence ≥ 5% in the total subjects) TEAEs in hematology variables neutrophil count increased (HLX14 group vs. US-Prolia group vs. EU-Prolia group vs. CN-Prolia group: 17.2% vs. 12.3% vs. 5.4% vs. 14.0%), white blood cell count increased (13.8% vs. 7.0% vs. 3.6% vs. 3.5%), neutrophil count decreased (12.1% vs. 12.3% vs. 16.1% vs. 15.8%), white blood cell count decreased (10.3% vs. 15.8% vs. 10.7% vs. 10.5%), lymphocyte count decreased (6.9% vs. 5.3% vs. 7.1% vs. 3.5%), and neutrophil percentage increased (3.4% vs. 8.8% vs. 5.4% vs. 8.8%).

The most common (incidence ≥ 5% in the total subjects) TEAEs in serum chemistry variables were blood calcium increased (HLX14 group vs. US-Prolia group vs. EU-Prolia group vs. CN-Prolia group: 29.3% vs. 28.1% vs. 28.6% vs. 12.3%), blood triglycerides increased (24.1% vs. 21.1% vs. 21.4% vs. 17.5%), blood phosphorus decreased (22.4% vs. 22.8% vs. 19.6% vs. 26.3%), alanine aminotransferase increased (19.0% vs. 15.8% vs. 28.6% vs. 19.3%), blood cholesterol increased

(17.2% vs. 21.1% vs. 17.9% vs. 8.8%), aspartate aminotransferase increased (13.8% vs. 14.0% vs. 14.3% vs. 17.5%), blood creatinine increased (13.8% vs. 8.8% vs. 8.9% vs. 14.0%), blood uric acid increased (10.3% vs. 10.5% vs. 16.1% vs. 12.3%), and blood calcium decreased (5.2% vs. 12.3% vs. 12.5% vs. 14.0%).

The most common (incidence ≥ 5% in the total subjects) TEAE in urinalysis variables was protein urine present (HLX14 group vs. US-Prolia group vs. EU-Prolia group vs. CN-Prolia group: 19.0% vs. 8.8% vs. 12.5% vs. 14.0%).

Study HLX14-002-PMOP301

The most common (incidence ≥ 1% in the total subjects) TEAEs in hematology variables under the SOC of Investigations by PT were white blood cell count decreased (HLX14 group vs. Prolia group: 2.7% vs. 1.2%) and neutrophil count decreased (1.6% vs. 1.6%).

The most common (incidence ≥ 1% in the total subjects) TEAEs in serum chemistry variables were alanine aminotransferase increased (HLX14 group vs. Prolia group: 3.9% vs. 3.1%), blood glucose increased (3.9% vs. 2.7%), aspartate aminotransferase increased (2.7% vs. 1.9%), blood alkaline phosphatase decreased (2.7% vs. 1.2%), blood creatinine increased (2.7% vs. 0.8%), gamma-glutamyltransferase increased (1.2% vs. 2.7%), blood uric acid increased (1.2% vs. 0.8%), and blood bilirubin increased (0.8% vs. 2.3%).

The most common (incidence ≥ 1% in the total subjects) TEAEs in urinalysis were urinary occult blood positive (HLX14 group vs. Prolia group: 5.5% vs. 5.0%), white blood cells urine positive (3.9% vs. 3.5%), protein urine present (0.8% vs. 2.7%), and red blood cells urine positive (0.8% vs. 1.9%).

The most common (incidence ≥ 1% in the total subjects) TEAEs in coagulation variables were fibrin D-dimer increased (HLX14 group vs. Prolia group: 3.5% vs. 3.1%) and prothrombin time shortened (0.4% vs. 1.9%).

The TEAEs in 25-(OH) vitamin D variables was vitamin D decreased (HLX14 group vs. Prolia group: 0.4% vs. 0.8%).

2.5.8.5. Immunological events

The applicant has established and validated a state of the art ECL based 3 tiered ADA assay to assess anti-HLX14 and anti-Prolia antibodies.

The method is based on HLX14 labelled with biotin and sulfo and uses the classical bridging principle to detect antibodies against HLX14 and anti-Prolia in human serum. Ruthenium in the complex "biotinylated- HLX14-ADA- HLX14-ruthenylated" emits light at 620 nm, which is measured after stimulation by the MSD Sector Image. Measured signal intensity is directly proportional to the ADA content in the sample. Methodology for screening and confirmation cut-point determination was described and seems acceptable. Critical reagents, lot numbers and expiry dates were listed. All critical reagents were within their shelf life during validation study. Pooled human serum of 36 individual normal male human serum specimens was used as negative control. Screening and confirmation sensitivities were assessed in serum matrix. Precision and robustness were assessed. No Hook-effect or matrix effect influence by normal human serum, lipemic serum or hemolytic serum was observed. 200 µg/mL was reported as the drug tolerance level. Target interference level was found at 17.6 ng/ml RANKL. Sample stability was confirmed for 72 hours at room temperature and 9 freeze/thaw cycles. Long term stability was confirmed initially for 1 month at -20 and -70°C, and for 6 months as reported in a first amendment to the study report. In a second amendment, inaccurate descriptions in the original report were corrected. One year stability assessment is still ongoing.

Taken together, method for the detection of anti-HLX14 and anti-Prolia antibodies in human serum in the bridge assay format with the MSD platform seems suitable for the intended use.

The applicant has established and validated a functional assay for detection of anti-HLX14 and Prolia neutralizing antibodies in human serum.

In brief, neutralising potential of induced antibodies was assessed by a functional cell based assay. HEK293 cell line was transfected with a plasmid containing RANK receptor and NF-κB gene linked to luciferase. Presence of HLX14 prevents the interaction between RANKL and RANK receptor leading to cell inactivation. If testing samples contain NAbs against HLX14, RANKL will interact with RANK receptor on HEK293 cells and activate the NF-κB signal pathway, leading to the expression of luciferase. To reduce drug interference, a pretreatment step is performed using a Bead Extraction with Acid Dissociation. Validation included: cut point determination, sensitivity, LPC determination, hook effect, precision, robustness, selectivity, drug tolerance, RANKL target interference and stability.

Taken together, presented method for Nab assessment seems suitable for the intended use.

A summary of immunogenicity results (ADAs and Nabs) as well as the influence of anti-drug antibodies on Pharmacokinetics and Pharmacodynamics are presented and discussed in section 3.3.1. of this AR.

Below is presented an overview of safety events in ADA-positive subjects of studies HLX14-001 and HLX14-002-PMOP301. Of note, no positive ADA samples were observed for any subject in part I of study HLX14-001.

Table 36. Summary of TEAEs by ADA status

	HLX14-001 Part2 (N=228)					HLX14-002-PMOP301 (N=506)	
System Organ Class Preferred term	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Prolia® Total (N=170)	HLX14 (N=252)	Prolia® (N=254)
ADA Positive, n (%)	6 (10.3)	10 (17.5)	13 (23.2)	12 (21.1)	35 (20.6)	28 (11.1)	35 (13.8)
Number of subjects experiencing at least one adverse event, n (%)	6 (100)	10 (100)	13 (100)	12 (100)	35 (100)	25 (89.3)	32 (91.4)
ADA Negative, n (%)	52 (89.7)	47 (82.5)	43 (76.8)	45 (78.9)	135 (79.4)	224 (88.9)	219 (86.2)
Number of subjects experiencing at least one adverse event, n (%)	52 (100)	47 (100)	43 (100)	45 (100)	135 (100)	197 (87.9)	193 (88.1)

N is the number of patients with overall ADA positive or negative.
Overall positive/negative rate is calculated based on the total number of patients with at least one testing result post-dose administration. Other n(%) is calculated based on n of ADA Positive/Negative.
Overall ADA positive is defined as at least one post-baseline ADA positive.
[Source: t_adae_socpt_ada_bystudy.sas] 15MAR2024T10:55:29

Table 37. Summary of TEAEs with CTCAE Grade ≥3 by ADA status

	HLX14-001 Part2 (N=228)					HLX14-002-PMOP301 (N=506)	
System Organ Class Preferred term	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Prolia® Total (N=170)	HLX14 (N=252)	Prolia® (N=254)
ADA Positive, n (%)	6 (10.3)	10 (17.5)	13 (23.2)	12 (21.1)	35 (20.6)	28 (11.1)	35 (13.8)
Number of subjects experiencing at least one adverse event with CTCAE Grade >=3, n (%)	1 (16.7)	0	0	0	0	0	3 (8.6)
ADA Negative, n (%)	52 (89.7)	47 (82.5)	43 (76.8)	45 (78.9)	135 (79.4)	224 (88.9)	219 (86.2)
Number of subjects experiencing at least one adverse event with CTCAE Grade >=3, n (%)	2 (3.8)	6 (12.8)	6 (14.0)	2 (4.4)	14 (10.4)	24 (10.7)	16 (7.3)

N is the number of patients with overall ADA positive or negative.
Overall positive/negative rate is calculated based on the total number of patients with at least one testing result post-dose administration. Other n(%) is calculated based on n of ADA Positive/Negative.
Overall ADA positive is defined as at least one post-baseline ADA positive.
[Source: t_adae_socpt_ada_bystudy.sas] 15MAR2024T10:55:31

Table 38. Summary of Denosumab-Related TEAEs with CTCAE Grade ≥3 by ADA status

	HLX14-001 Part2 (N=228)					HLX14-002-PMOP301 (N=506)	
System Organ Class Preferred term	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Prolia® Total (N=170)	HLX14 (N=252)	Prolia® (N=254)
ADA Positive, n (%)	6 (10.3)	10 (17.5)	13 (23.2)	12 (21.1)	35 (20.6)	28 (11.1)	35 (13.8)
Number of subjects experiencing at least one Denosumab related adverse event with CTCAE Grade >=3, n (%)	1 (16.7)	0	0	0	0	0	0
ADA Negative, n (%)	52 (89.7)	47 (82.5)	43 (76.8)	45 (78.9)	135 (79.4)	224 (88.9)	219 (86.2)
Number of subjects experiencing at least one Denosumab related adverse event with CTCAE Grade >=3, n (%)	1 (1.9)	4 (8.5)	1 (2.3)	0	5 (3.7)	1 (0.4)	0

N is the number of patients with overall ADA positive or negative.
Overall positive/negative rate is calculated based on the total number of patients with at least one testing result post-dose administration. Other n(%) is calculated based on n of ADA Positive/Negative.
Overall ADA positive is defined as at least one post-baseline ADA positive.
[Source: t_adae_socpt_ada_bystudy.sas] 15MAR2024T10:55:32

Table 39. Summary of Serious TEAEs by ADA status

	HLX14-001 Part2 (N=228)					HLX14-002-PMOP301 (N=506)	
System Organ Class Preferred term	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Prolia® Total (N=170)	HLX14 (N=252)	Prolia® (N=254)
ADA Positive, n (%)	6 (10.3)	10 (17.5)	13 (23.2)	12 (21.1)	35 (20.6)	28 (11.1)	35 (13.8)
Number of subjects experiencing at least one serious adverse event, n (%)	0	0	0	0	0	0	2 (5.7)
ADA Negative, n (%)	52 (89.7)	47 (82.5)	43 (76.8)	45 (78.9)	135 (79.4)	224 (88.9)	219 (86.2)
Number of subjects experiencing at least one serious adverse event, n (%)	0	2 (4.3)	0	0	2 (1.5)	22 (9.8)	14 (6.4)

N is the number of patients with overall ADA positive or negative.
Overall positive/negative rate is calculated based on the total number of patients with at least one testing result post-dose administration. Other n(%) is calculated based on n of ADA Positive/Negative.
Overall ADA positive is defined as at least one post-baseline ADA positive.
[Source: t_adae_socpt_ada_bystudy.sas] 15MAR2024T10:55:34

Table 40. Summary of AESI by ADA status

	HLX14-001 Part2 (N=228)					HLX14-002-PMOP301 (N=506)	
System Organ Class Preferred term	HLX14 (N=58)	US-Prolia® (N=57)	EU-Prolia® (N=56)	CN-Prolia® (N=57)	Prolia® Total (N=170)	HLX14 (N=252)	Prolia® (N=254)
ADA Positive, n (%)	6 (10.3)	10 (17.5)	13 (23.2)	12 (21.1)	35 (20.6)	28 (11.1)	35 (13.8)
At least one AESI, n (%)	0	1 (10.0)	1 (7.7)	2 (16.7)	4 (11.4)	1 (3.6)	3 (8.6)
ADA Negative, n (%)	52 (89.7)	47 (82.5)	43 (76.8)	45 (78.9)	135 (79.4)	224 (88.9)	219 (86.2)
At least one AESI, n (%)	4 (7.7)	8 (17.0)	8 (18.6)	7 (15.6)	23 (17.0)	9 (4.0)	13 (5.9)

N is the number of patients with overall ADA positive or negative.
Overall positive/negative rate is calculated based on the total number of patients with at least one testing result post-dose administration. Other n(%) is calculated based on n of ADA Positive/Negative.
Overall ADA positive is defined as at least one post-baseline ADA positive.
[Source: t_adae_socpt_ada_bystudy.sas] 15MAR2024T10:55:36

2.5.8.6. Safety related to drug-drug interactions and other interactions

Not applicable

2.5.8.7. Discontinuation due to adverse events

Study HLX14-001

No TEAEs leading to drug discontinuation were reported in part I or II of the study.

Study HLX14-002-PMOP301

Only 3 (1.2%) subjects in the Prolia group experienced TEAEs leading to **drug discontinuation**, the PTs were gingival cyst, toothache, periodontitis, and cervix carcinoma. Only 1 (0.4%) subject in the Prolia group experienced a Prolia-related AE leading to drug discontinuation, and the PT was toothache.

Table 41. Summary of TEAEs Leading to Drug Discontinuation by SOC and PT (SS)

System Organ Class Preferred Term	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Any TEAEs leading to drug discontinuation, n (%) E [1]	0	3 (1.2) 4	3 (0.6) 4
Gastrointestinal disorders, n (%) E	0	2 (0.8) 2	2 (0.4) 2
Gingival cyst	0	1 (0.4) 1	1 (0.2) 1
Toothache	0	1 (0.4) 1	1 (0.2) 1
Infections and infestations, n (%) E	0	1 (0.4) 1	1 (0.2) 1
Periodontitis	0	1 (0.4) 1	1 (0.2) 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%) E	0	1 (0.4) 1	1 (0.2) 1
Cervix carcinoma	0	1 (0.4) 1	1 (0.2) 1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
E: Events.
AE: Adverse Event; TEAE: Treatment Emergent Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events
[1] TEAE was defined as an AE that first occurs or worsens in severity in the period from the first dose administrated date to Week 52 or to the end for the subjects who end the study before Week 52.
System Organ Class and Preferred Term were coded using MedDRA version 26.1.
Data source: Module 5.3.5.3 HLX14-002-PMOP301 CSR, Table 12-10.

Table 42. Summary of HLX14/Prolia-related AEs Leading to Drug Discontinuation by SOC and PT (SS)

System Organ Class Preferred Term	HLX14 (N=257)	Prolia® (N=257)	Total (N=514)
Any TEAEs leading to drug discontinuation, n (%) E [1]	0	1 (0.4) 1	1 (0.2) 1
Gastrointestinal disorders, n (%) E	0	1 (0.4) 1	1 (0.2) 1
Toothache	0	1 (0.4) 1	1 (0.2) 1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
E: Events.
AE: Adverse Event; TEAE: Treatment Emergent Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events.
[1] TEAE was defined as an AE that first occurs or worsens in severity in the period from the first dose administrated date to Week 52 or to the end for the subjects who end the study before Week 52.
System Organ Class and Preferred Term were coded using MedDRA version 26.1.
Data source: Module 5.3.5.1 HLX14-002-PMOP301 CSR, Table 12-11.

A total of 13 (2.5%) subjects experienced TEAEs leading to **drug interruption**, including 8 (3.1%) subjects in the HLX14 group and 5 (1.9%) subjects in the Prolia group. The most common TEAE leading to drug interruption (incidence ≥ 1% in the total subjects) by PT was urinary tract infection (HLX14 group vs. Prolia group: 1.6% vs. 1.2%). No other TEAEs leading to drug interruption were reported for more than 1 subject in either treatment group.

Table 43. Summary of TEAEs Leading to Drug Interruption by SOC and PT (SS)

System Organ Class Preferred Term	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Any TEAEs leading to drug interruption, n (%) E [1]	8 (3.1) 9	5 (1.9) 7	13 (2.5) 16
Infections and infestations, n (%) E	4 (1.6)4	4 (1.6) 6	8 (1.6) 10
Urinary tract infection	4 (1.6)4	3 (1.2) 4	7 (1.4) 8
Pneumonia	0	1 (0.4)1	1 (0.2) 1
Septic shock	0	1 (0.4) 1	1 (0.2) 1
Gastrointestinal disorders, n (%) E	2 (0.8) 2	0	2 (0.4) 2
Chronic gastritis	1 (0.4) 1	0	1 (0.2) 1
Toothache	1 (0.4) 1	0	1 (0.2) 1
Injury, poisoning and procedural complications, n (%) E	1 (0.4) 1	0	1 (0.2) 1
Humerus fracture	1 (0.4) 1	0	1 (0.2) 1
Investigations, n (%) E	1 (0.4) 1	0	1 (0.2) 1
White blood cell counts increased	1 (0.4) 1	0	1 (0.2) 1
Renal and urinary disorders, n (%) E	1 (0.4) 1	0	1 (0.2) 1
Ureterolithiasis	1 (0.4) 1	0	1 (0.2) 1
Skin and subcutaneous tissue disorders, n (%) E	0	1 (0.4) 1	1 (0.2) 1
Dermatitis	0	1 (0.4) 1	1 (0.2) 1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
E: Events.
AE: Adverse Event; TEAE: Treatment Emergent Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events.
[1] TEAE was defined as an AE that first occurs or worsens in severity in the period from the first dose administrated date to Week 52 or to the end for the subjects who end the study before Week 52.
System Organ Class and Preferred Term were coded using MedDRA version 26.1.
Data source: Module 5.3.5.1 HLX14-002-PMOP301 CSR, Table 12-12.

Regarding **HLX14/Prolia-related AEs leading to drug interruption** a total of 4 (0.8%) subjects experienced HLX14/Prolia-related AEs leading to drug interruption, including 1 (0.4%) subject in the HLX14 group and 3 (1.2%) subjects in the Prolia group. The HLX14/Prolia-related AEs leading to drug interruption by PT were urinary tract infection (HLX14 group vs. Prolia group: 0.4% vs. 0.8%), and dermatitis (0 vs. 0.4%).

Table 44. Summary of HLX14/Prolia-related AEs Leading to Drug Interruption by SOC and PT (SS)

System Organ Class Preferred Term	HLX14 (N=256)	Prolia® (N=258)	Total (N=514)
Any HLX14/Prolia-related AEs leading to drug interruption, n (%) E [1]	1 (0.4) 1	3 (1.2) 4	4 (0.8) 5
Infections and infestations, n (%) E	1 (0.4) 1	2 (0.8) 3	3 (0.6) 4
Urinary tract infection	1 (0.4) 1	2 (0.8) 3	3 (0.6) 4
Skin and subcutaneous tissue disorders, n (%) E	0	1 (0.4) 1	1 (0.2) 1
Dermatitis	0	1 (0.4) 1	1 (0.2) 1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
E: Events.
AE: Adverse Event; TEAE: Treatment Emergent Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events.
[1] TEAE was defined as an AE that first occurs or worsens in severity in the period from the first dose administrated date to Week 52 or to the end for the subjects who end the study before Week 52.

System Organ Class and Preferred Term were coded using MedDRA version 26.1.
Data source: Module 5.3.5.1 HLX14-002-PMOP301 CSR, Table 12-13.

Summary of treatment period 2 – Extension Safety Set (week 52 – week78)

Table 45. Summary of HLX14/Prolia treatment exposure and compliance – Week 52-78 (Extension Safety Set)

	HLX14/HLX14 (N=220)	Prolia®/HLX14 (N=110)	Prolia®/Prolia® (N=110)
Total exposure days, (days) [1]			
n	220	110	110
Mean (SD)	1.0 (0)	1.0 (0)	1.0 (0)
Median (Min, Max)	1.0 (1, 1)	1.0 (1, 1)	1.0 (1, 1)
Cumulative dose, (mg) [2]			
n	220	110	110
Mean (SD)	60.0 (0)	60.0 (0)	60.0 (0)
Median (Min, Max)	60.0 (60, 60)	60.0 (60, 60)	60.0 (60, 60)
Treatment compliance, (%) [3]			
n	220	110	110
Mean (SD)	100.0 (0)	100.0 (0)	100.0 (0)
Median (Min, Max)	100.0 (100, 100)	100.0 (100, 100)	100.0 (100, 100)
Number of injections received, n (%)			
1	220 (100)	110 (100)	110 (100)

Summary of the treatment exposure and compliance for subjects in treatment period 2 (from Week 52 to Week 78), dose on Week 52 was included.
[1] Total exposure days = (date of last dose in specific treatment period - date of first dose in specific treatment period + 1).
[2] Cumulative dose (mg): The cumulative dose per subject in a period was the sum of the total dosage that the subject received.
[3] Treatment compliance (%) = Sum of actual cumulative dosage/Sum of planned dosage*100%.

Table 46. Summary of Treatment Emergent Adverse Events (TEAEs) - Week 52-78 (Extension Safety Set)

	HLX14/HLX14 (N=220)	Prolia®/HLX14 (N=110)	Prolia®/Prolia® (N=110)	Total (N=440)
Any TEAEs, n (%) E [1]	153 (69.5) 403	84 (76.4) 240	79 (71.8) 224	316 (71.8) 867

Maximum CTCAE grade for any TEAEs, n (%) E				
Grade 1	108 (49.1) 328	64 (58.2) 201	57 (51.8) 166	229 (52.0) 695
Grade 2	39 (17.7) 66	19 (17.3) 37	16 (14.5) 50	74 (16.8) 153
Grade 3	5 (2.3) 8	1 (0.9) 2	5 (4.5) 7	11 (2.5) 17
Grade 4	1 (0.5) 1	0	1 (0.9) 1	2 (0.5) 2
Grade 5	0	0	0	0
Any treatment-related AEs, n (%) E [2]	25 (11.4) 33	14 (12.7) 24	15 (13.6) 15	54 (12.3) 72
Related to HLX14/Prolia	17 (7.7) 22	12 (10.9) 20	8 (7.3) 8	37 (8.4) 50
Related to Calcium	7 (3.2) 8	4 (3.6) 4	3 (2.7) 3	14 (3.2) 15
Related to Vitamin D	8 (3.6) 8	1 (0.9) 1	7 (6.4) 7	16 (3.6) 16
Any TEAEs with CTCAE grade ≥ 3, n (%) E	6 (2.7) 9	1 (0.9) 2	6 (5.5) 8	13 (3.0) 19
Any treatment-related AEs with CTCAE grade ≥ 3, n (%) E	0	0	0	0
Related to HLX14/Prolia	0	0	0	0
Related to Calcium	0	0	0	0
Related to Vitamin D	0	0	0	0
Any injection site reaction, n (%) E	0	0	0	0
Any AE of Special Interest (AESI), n (%) E	4 (1.8) 4	1 (0.9) 1	4 (3.6) 4	9 (2.0) 9
Hypersensitivity Reaction	0	0	0	0
Hypocalcaemia	3 (1.4) 3	1 (0.9) 1	2 (1.8) 2	6 (1.4) 6
Serious Infection	1 (0.5) 1	0	2 (1.8) 2	3 (0.7) 3
Osteonecrosis of the Jaw	0	0	0	0
Atypical Femoral Fracture	0	0	0	0
Any HLX14/Prolia-related AE of Special Interest (AESI), n (%) E	2 (0.9) 2	1 (0.9) 1	1 (0.9) 1	4 (0.9) 4
Hypersensitivity Reaction	0	0	0	0
Hypocalcaemia	2 (0.9) 2	1 (0.9) 1	1 (0.9) 1	4 (0.9) 4
Serious Infection	0	0	0	0
Osteonecrosis of the Jaw	0	0	0	0
Atypical Femoral Fracture	0	0	0	0
Any AESI with CTCAE grade ≥ 3, n (%) E	1 0.5) 1	0	2 (1.8) 2	3 (0.7) 3
Hypersensitivity Reaction	0	0	0	0
Hypocalcaemia	0	0	0	0
Serious Infection	1 (0.5) 1	0	2 (1.8) 2	3 (0.7) 3
Osteonecrosis of the Jaw	0	0	0	0
Atypical Femoral Fracture	0	0	0	0
Any HLX14/Prolia-related AESI with CTCAE grade ≥ 3, n (%) E	0	0	0	0
Hypersensitivity Reaction	0	0	0	0
Hypocalcaemia	0	0	0	0
Serious Infection	0	0	0	0
Osteonecrosis of the Jaw	0	0	0	0

Atypical Femoral Fracture	0	0	0	0
Any serious AESI, n (%) E	1 (0.5) 1	0	2 (1.8) 2	3 (0.7) 3
Hypersensitivity Reaction	0	0	0	0
Hypocalcaemia	0	0	0	0
Serious Infection	1 (0.5) 1	0	2 (1.8) 2	3 (0.7) 3
Osteonecrosis of the Jaw	0	0	0	0
Atypical Femoral Fracture	0	0	0	0
Any HLX14/Prolia-related serious AESI, n (%) E	0	0	0	0
Hypersensitivity Reaction	0	0	0	0
Hypocalcaemia	0	0	0	0
Serious Infection	0	0	0	0
Osteonecrosis of the Jaw	0	0	0	0
Atypical Femoral Fracture	0	0	0	0
Any serious TEAEs, n (%) E	6 (2.7) 8	1 (0.9) 2	6 (5.5) 7	13 (3.0) 17
Any treatment-related serious AEs, n (%) E	0	0	0	0
Related to HLX14/Prolia	0	0	0	0
Related to Calcium	0	0	0	0
Related to Vitamin D	0	0	0	0
Any TEAEs leading to death, n (%) E	0	0	0	0
Any treatment-related AEs leading to death, n (%) E	0	0	0	0
Related to HLX14/Prolia	0	0	0	0
Related to Calcium	0	0	0	0
Related to Vitamin D	0	0	0	0
Any TEAEs leading to drug discontinuation [3], n (%) E	0	0	0	0
Any treatment-related AEs leading to drug discontinuation, n (%) E	0	0	0	0
Related to HLX14/Prolia	0	0	0	0
Related to Calcium	0	0	0	0
Related to Vitamin D	0	0	0	0
Any TEAEs leading to drug interruption [3], n (%) E	0	0	0	0
Any treatment-related AEs leading to drug interruption, n (%) E	0	0	0	0
Related to HLX14/Prolia	0	0	0	0
Related to Calcium	0	0	0	0
Related to Vitamin D	0	0	0	0

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
E: Events.
AE: Adverse Event; TEAE: Treatment-Emergent Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events.
[1] TEAE for Treatment period 2 ("from Week 52 to Week 78") was defined as an AE that first occurred or worsened in severity in the period from the third dose administrated date to the end for the subjects who entered the treatment period 2.
[2] Any treatment-related AEs was defined as the TEAE related to HLX14/Prolia or Calcium or Vitamin D.

[3] drug discontinuation/interruption means HLX14/Prolia discontinuation/interruption.
AESIs in this study included: hypersensitivity reactions, hypocalcaemia, serious infections (including skin infections), osteonecrosis of the jaw and atypical femoral fracture. For further information, please see the AESI summary table by PT and SOC.

Table 47. Summary of HLX14/Prolia-related Adverse Events by SOC and PT - Week 52-78 (Extension Safety Set)

System Organ Class Preferred Term	HLX14/HLX14 (N=220)	Prolia®/HLX14 (N=110)	Prolia®/Prolia® (N=110)	Total (N=440)
Subjects with at least one HLX14/Prolia-related AE, n (%) E [1]	17 (7.7) 22	12 (10.9) 20	8 (7.3) 8	37 (8.4) 50
Metabolism and nutrition disorders, n (%) E	8 (3.6) 8	5 (4.5) 9	4 (3.6) 4	17 (3.9) 21
Hypercholesterolaemia	2 (0.9) 2	3 (2.7) 3	0	5 (1.1) 5
Hypocalcaemia	2 (0.9) 2	1 (0.9) 1	1 (0.9) 1	4 (0.9) 4
Hyperlipidaemia	1 (0.5) 1	1 (0.9) 1	1 (0.9) 1	3 (0.7) 3
Hypophosphataemia	0	1 (0.9) 1	2 (1.8) 2	3 (0.7) 3
Hypercalcaemia	1 (0.5) 1	1 (0.9) 1	0	2 (0.5) 2
Hypertriglyceridaemia	2 (0.9) 2	0	0	2 (0.5) 2
Hyperphosphataemia	0	1 (0.9) 1	0	1 (0.2) 1
Hyponatraemia	0	1 (0.9) 1	0	1 (0.2) 1
Investigations, n (%) E	6 (2.7) 6	4 (3.6) 4	0	10 (2.3) 10
White blood cell count decreased	1 (0.5) 1	1 (0.9) 1	0	2 (0.5) 2
Blood creatinine increased	1 (0.5) 1	0	0	1 (0.2) 1
Electrocardiogram ST segment abnormal	1 (0.5) 1	0	0	1 (0.2) 1
Electrocardiogram ST-T segment abnormal	0	1 (0.9) 1	0	1 (0.2) 1
Fibrin D dimer increased	0	1 (0.9) 1	0	1 (0.2) 1
Full blood count decreased	1 (0.5) 1	0	0	1 (0.2) 1
Gamma-glutamyltransferase increased	1 (0.5) 1	0	0	1 (0.2) 1
Urinary occult blood positive	0	1 (0.9) 1	0	1 (0.2) 1
White blood cells urine positive	1 (0.5) 1	0	0	1 (0.2) 1
Infections and infestations, n (%) E	3 (1.4) 3	2 (1.8) 2	1 (0.9) 1	6 (1.4) 6
Urinary tract infection	3 (1.4) 3	2 (1.8) 2	1 (0.9) 1	6 (1.4) 6
Cardiac disorders, n (%) E	2 (0.9) 3	0	2 (1.8) 2	4 (0.9) 5
Sinus bradycardia	2 (0.9) 3	0	2 (1.8) 2	4 (0.9) 5
Gastrointestinal disorders, n (%) E	1 (0.5) 1	1 (0.9) 1	1 (0.9) 1	3 (0.7) 3
Toothache	1 (0.5) 1	1 (0.9) 1	1 (0.9) 1	3 (0.7) 3
Musculoskeletal and connective tissue disorders, n (%) E	0	2 (1.8) 4	0	2 (0.5) 4
Muscle spasms	0	1 (0.9) 2	0	1 (0.2) 2
Osteitis condensans	0	1 (0.9) 1	0	1 (0.2) 1
Spinal osteoarthritis	0	1 (0.9) 1	0	1 (0.2) 1
General disorders and administration site conditions, n (%) E	1 (0.5) 1	0	0	1 (0.2) 1
Fatigue	1 (0.5) 1	0	0	1 (0.2) 1

N: The number of subjects in the analysis set; n: The number of subjects in specific category; %: (n/N*100).
E: Events.
AE: Adverse Event; TEAE: Treatment-Emergent Adverse Event.
[1] TEAE for Treatment period 2 ("from Week 52 to Week 78") was defined as an AE that first occurred or worsened in severity in the period from the third dose administrated date to the end for the subjects who entered the treatment period 2.
System Organ Class and Preferred Term were coded using MedDRA version 27.0.

No subjects died during the treatment period 2.

No subjects experienced **injection site reactions**, TEAEs leading to drug discontinuation or **TEAEs leading to drug interruption** during the treatment period 2.

A total of 4 (0.9%) subjects experienced **HLX14 or Prolia-related AESIs**, including 2 (0.9%) subjects in the HLX14/HLX14 group, 1 (0.9%) subject in the Prolia/HLX14 group and 1 (0.9%) subject in the Prolia/Prolia group. The HLX14 or Prolia-related AESI by PT was hypocalcaemia (HLX14/HLX14 group vs. Prolia/HLX14 group vs. Prolia/Prolia group: 0.9% vs. 0.9% vs. 0.9%).

No subjects experienced Grade ≥ 3 HLX14 or Prolia-related AESIs and no subjects experienced **HLX14 or Prolia-related serious AESIs** during the treatment period 2.

The **calcium and Vitamin D exposure** levels were comparable among the HLX14/HLX14 group, the Prolia/HLX14 group and the Prolia/Prolia group.

2.5.8.8. Post marketing experience

Not applicable

2.5.9. Discussion on clinical safety

The applicant submitted safety data from two clinical studies, HLX14-001 and HLX14-002-PMOP301. HLX14-001 was conducted in healthy males, whereas study HLX14-002-PMOP301 was conducted in postmenopausal women with osteoporosis at high risk of fracture (PMO patients). Consequently, it is appropriate to report safety data separately for each study as they were conducted in different populations. The overall design of the clinical studies is considered adequate for a comprehensive safety and immunogenicity assessment of HLX14. The safety assessments performed during Studies HLX14-001 and HLX14-002-PMOP301 were designed to capture the known safety issues listed in the Prolia and Xgeva labels and are considered acceptable. The number of healthy subjects and PMO patients in the safety data set is deemed adequate for assessment of comparable safety of HLX14 with Prolia. Demographics and baseline characteristics were overall balanced between the treatment groups in both studies. According to the important known risks of hypocalcemia related to Prolia and Xgeva, special precautions were taken in both studies, which is acknowledged. These precautions included, among other things, supplementation with calcium and vitamin D and monitoring of calcium levels. Furthermore, in study HLX14-002-PMOP301 subjects with hypocalcemia and vitamin D deficiency were excluded from the study. However, in study HLX14-001 subjects with abnormal calcium levels were specifically excluded, whereas it is unclear whether subjects with vitamin D deficiency were also excluded. However, no concern regarding biosimilarity is apparent from this aspect. The majority of subjects enrolled in both studies were Asian. Within the scientific advice, the applicant was asked to include a discussion on ethic issues supporting the study data extrapolation between different ethnic groups (EU population vs non-EU population). The comprehensive justification discussed the published studies, PI and the globally approved clinical use of the reference medicinal product, dietary factors, physical activity, sun exposure, medical practice etc. The applicant states that the data and evidence presented support that the results/findings observed between the reference product Prolia and HLX14 in an Asian population can be reasonably generalized to a non-Asian population. This is considered acceptable from safety point of view.

In study HLX14-001 part I, 100% (n=24) of all enrolled subjects received their designated single dose and were thus included in the safety set. In part II a total of 228 subjects were enrolled and

randomized, 100% were treated. Fifteen subjects (6,6%) discontinued from the study. All subjects that were enrolled in part I or II were also included in the FAS and SS.

In study HLX14-002-PMOP301, 514 patients were randomized and treated. The majority completed the week 26 treatment (91.6% of all) and the study at week 52 (92.2% of all), with no notable imbalance between treatment arms.

Adverse Events

AEs of study HLX14-001 were collected for 274 after single dose or the time of subject's withdrawal from the study (whichever occurs first) and AEs were judged by the investigator regarding severity, seriousness, possible relatedness and classification as event of special interest. The reporting strategy is acknowledged. Conclusions on clinical safety from study HLX14-001 part I are compromised due to the very limited number of subjects included (n=12 per treatment arm) and the open-label study design. All subjects were healthy males and a single study drug injection (HLX14 and EU-Prolia) was given in part I. All subjects have experienced a TEAE, 91.7% have experienced a treatment-related AE (10 and 12 of the subjects treated with HLX14 and Prolia, respectively). All subjects in study HLX14-001 part II have experienced a TEAE after the single study drug injection (HLX14 and EU-, US-, or CN-Prolia) was given. Minor imbalances are reported for some of the PTs across the 4 study treatments, but no pattern of concern could be identified that would indicate general safety concerns or doubts regarding biosimilarity of HLX14 to EU-Prolia. The same conclusion also holds for treatment-related AEs. SOCs and PTs in imbalance across treatment groups (e.g. SOC Musculoskeletal and connective tissue disorders with 10.3%, 8.8% 17.9% and 0% of subjects with event after exposure to HLX14, US-, EU-, or CN-Prolia, respectively) do not question the general safety of HLX14 or the biosimilarity to (EU-)Prolia. No treatment-related event of grade ≥3 was reported by more than one subject of the same treatment group.

AEs in study HLX14-002-PMOP301 were recorded throughout the study. Only serious adverse events (SAEs) related to the study drug were followed up also after end of week 52 as noted in the respective CSR. It is critically noted that per protocol follow-up was intended for all adverse events after treatment or study termination until recovery (or return to baseline level), stable condition (no further improvement or worsening) or the subject was lost to follow-up. Still, the restriction of follow-up to serious events appears acceptable. The applicant presents safety data as treatment emergent adverse events (TEAE) and as treatment-related adverse events (TRAEs). A TEAEs was defined as an AE that first occurred or worsened in severity in the period from the first dose administrated date to Week 52 or to the end for the subjects who ended the study before Week 52. The categorization of TRAEs is based on a causality assessment of the investigator (required for all AEs) that is intended to conclude from "reasonable possibilities of the investigational products leading or contributing to the occurrence of this AE, and the facts (evidence) or arguments that prove the causality should usually be provided" as per study protocol. This categorization is acknowledged. Importantly, treatment-related also refers to a concluded (possible) relation to the calcium or vitamin D treatment besides study drug treatment (i.e. HLX14/Prolia) and thus does not allow for a direct relation to the study drug. For further clarity, the applicant also reports exclusive HLX14/Prolia-related adverse events. The approach is acceptable. Adverse drug reactions were not categorized as such, but HLX14/Prolia-related adverse events are sufficient to compare safety events with suspected causal relation to the study treatment. No further categorization of safety events is deemed required to conclude on the direct comparison of safety profiles of both treatment arms. No concerns regarding the risk of fractures arises as the rate of fractures during the study was well balanced between both study groups (n=10 fractures rated as TEAE per study group, HLX14 PTs: 3 spinal compression fractures, 2 humerus fractures, 1 rib fracture,

2 thoracic vertebral fractures, 1 femoral neck fracture, 1 forearm fracture; Prolia PTs: Prolia PTs: 6 spinal compression fractures, 1 rib fracture, 1 ankle fracture, 1 lumbar vertebral fracture, 1 patella fracture). AEs related to HLX14/Prolia were reported in a slightly higher proportion of subjects treated with Prolia (20.3% and 24.8% for HLX14 and Prolia, respectively), but no relevant imbalance between treatment arms is identified for reported SOCs or PTs. Only the SOC Metabolism and nutrition disorder was reported in more than 5% of subjects of either treatment arm (10.2% and 11.2% for HLX14 and Prolia, respectively). TRAEs (which additionally including the relation to calcium and vitamin D treatment) showed a comparable pattern in both treatment arms (26.2% and 31% for HLX14 and Prolia, respectively). The applicant also describes three Grade ≥3 TRAEs (hyperlipidaemia and ureterolithiasis in the HLX14 arm and synovitis in the Prolia arm), of which only one event was a HLX14-related AE of Grade ≥3 (hyperlipidaemia), which has not resolved before study end. The other events were apparently both considered as related to calcium treatment. TEAEs of Grade ≥3 were also reported by a comparable proportion of subjects across both treatment arms (9.4% and 7.4% for HLX14 and Prolia, respectively) and without any relevant imbalanced noticed for respective SOCs or PTs. In total 7 fracture events were rated as TEAE with Grade ≥3, but the rate of fractures among treatment groups does not rise any concern regarding biosimilarity (HLX14 PTs: 2 humerus fractures, 1 femoral neck fracture, 1 thoracic vertebral fracture; Prolia PTs: 1 lumbar vertebral fracture, 1 patella fracture, 1 spinal compression fracture). No concerns arise from reported AEs of Grade ≥3.

Serious AEs, Deaths, AESIs, Discontinuations due to AEs and other relevant Safety events

In study HLX14-001 part I, 20.8% have experienced an AESI (all PT blood calcium decreased; 3 and 2 of the subjects treated with HLX14 and Prolia, respectively). No serious events or AEs leading to discontinuation or drug interruption and no deaths were reported. In study HLX14-001 part II, two subjects reported a serious AE (PTs infective arthritis and synovitis, both in the group treated with US-Prolia). The proportion of subjects reporting an AESI was lowest in the group treated with HLX14 (6.9%, 15.8%, 16.1%, 15.8% of subjects with event after exposure to HLX14, US-, EU-, or CN-Prolia, respectively) and almost all events were related to low calcium levels (PTs blood calcium decreased and Hypocalcaemia pooled: 6.9%, 14.1%, 16.1%, 15.8% of subjects with event after exposure to HLX14, US-, EU-, or CN-Prolia, respectively). The only other event was PT infective Arthritis reported by a subject exposed to US-Prolia, which was also reported as serious AE and the only reported serious AESI. No subject discontinued or interrupted the study drug and no death was reported. No concerns arise from reported serious AEs, AESIs or deaths in study HLX14-001.

Reported serious adverse events in postmenopausal women with osteoporosis at high risk of fracture as reported from study HLX14-002-PMOP301 do not give rise of concern regarding the proposed biosimilarity of both applied treatments (8.6% and 6.2% of subjects experienced a SAE while treatment with HXL14 and Prolia, respectively). Reported SOCs and PTs appear well balanced between treatment groups (imbalances do not exceed a difference of 2 subjects more/less) and only 1 subject experienced a treatment-related SAE (PT colitis, while subject was treated with HLX14), which was resolved 2 weeks later. No SAE was related to vitamin-D treatment and in total two events were related to the treatment with calcium (one event of PT ureterolithiasis in a subject treated with HLX14 and one event of PT synovitis in a subject treated with Prolia). These 2 calcium-related serious AEs were resolved a few days later after occurrence as well. In total 7 fracture events were rated as TEAE with Grade ⩾3, but the rate of fractures among treatment groups does not rise any concern regarding biosimilarity (HLX14 PTs: 2 humerus fractures, 1 femoral neck fracture, 1 thoracic vertebral fracture; Prolia PTs: 1 lumbar vertebral fracture, 1 patella fracture, 1 spinal compression fracture). It is further reassuring that no deaths have occurred during the study. Injection site reactions were reported only by a few patients and do not give rise to a concern. Similarly, hypersensitivity (PT dermatitis allergic)

was only reported by one patient in the Prolia group. Safety events to be reported as adverse events of special interest were hypersensitivity reactions, hypocalcemia, serious infections (including skin infection), osteonecrosis of the jaw and atypical femur fracture as per study protocol. AESIs as well as study-drug-related AESIs were reported by a higher proportion of subjects treated with Prolia compared to subjects treated with HLX14 (AESI/drug-related AESI: 3.9%/2.3% and 6.2%/4.7% of subjects treated with HLX14 and Prolia, respectively). This imbalance is especially related to cases of the PT hypocalcaemia (PT Hypocalcaemia as AESI/drug-related AESI: 2.7%/2.3% and 5%/4.3% of subjects treated with HLX14 and Prolia, respectively), whereas other PTs did not exceed a difference of 1 subject more/less between treatment groups. No concerns arise for the expected safety of HLX14 and the imbalance appears too small to conclude any critical concern regarding biosimilarity of both products. AESIs of grade ≥3 were more frequently reported in subjects treated with HLX14 compared to those treated with Prolia (i.e. 2-times more in a rather low frequency of 1.6% and 0.8% of subjects reported for HLX14 and Prolia, respectively), but the imbalance is mild (2 subjects) and none of the respective PTs was reported with an imbalance of more than 1 subject. All were in the SOC Infections and infestations. Similarly, also serious AESIs were rare (1.2% and 0.8% of subjects treated with HLX14 and Prolia, respectively) and were all reported for the SOC Infections and infestations without relevant imbalance in reported PTs. Narratives for subjects with relevant safety events were provided. No concern arises regarding the proposed biosimilarity of HLX14 and (EU-)Prolia from reported AEs of special interest, serious adverse events, deaths, injection site or hypersensitivity reactions.

It is acknowledged that no TEAEs leading to drug discontinuation were reported in part I or II of study HLX14-001. Treatment-related AEs as well as HLX14/Prolia-related AEs that lead to discontinuation of the study drugs during study HLX14-002-PMOP301 were only reported for subjects treated with Prolia (1.2% and 0.4%, respectively). No PT was reported twice as cause for discontinuation. No concerns arise for the expected safety of HLX14 and the imbalance appears too small to conclude any critical concern regarding biosimilarity of both products.

Laboratory data, vital signs, physical examination

Physical examinations, vital signs, laboratory tests (hematology, serum chemistry, and urinalysis); 12-lead electrocardiography (ECG) were evaluated in both studies. Vital signs in study HLX14-001 were evaluated at each visit. Physical examinations, laboratory findings and ECG were not evaluated at each visit but sufficiently throughout the whole study. Physical examinations, vital signs, laboratory tests (hematology, serum chemistry, and urinalysis), coagulation, 25-OH vitamin D, 12-lead electrocardiography (ECG) were assessed sufficiently throughout the study HLX14-002-PMOP301. Laboratory findings in both clinical trials did not reveal reactions that are typically related to denosumab, but not unexpected in a normal population (study HLX14-001) or in women with postmenopausal osteoporosis (study HLX14-002-PMOP301; such as blood glucose increase, ALT increase or neutrophil count decreased). Furthermore, there were no remarkable findings on vital signs, physical examination or ECG results in either study. Thus, biosimilarity between HLX14 and (EU-)Prolia can be concluded from reported laboratory data.

Treatment switch in period 2 from week 52 – week78

Safety data were also provided for a treatment period 2 of study HLX14-002-PMOP301 (week 52 to week 78). This treatment period consisted of a subpopulation that got a third dose of HLX14 (n=220) and of 220 subjects from the Prolia group, who have been re-randomized to switch treatment from Prolia to HLX14 (n=110) and to those who received a third dose of Prolia (n=110). A slightly higher proportion of TEAE were reported in this study period for the group switching treatment compared to

the other two groups (HLX14/HLX14: 69.5%, Prolia/HLX14: 76.4%, Prolia/Prolia: 71.8%) and also the proportion of related AEs seems mildly higher in this group (HLX14/HLX14: 7.7%, Prolia/HLX14: 10.9%, Prolia/Prolia: 7.3%). The only TEAEs with incidences ⩾5% and higher rates in the Prolia/HLX14 group were vitamin D deficiency (HLX14/HLX14: 7.7% vs. Prolia/HLX14: 15.5% vs. Prolia/Prolia: 8.2%) and urinary tract infection (HLX14/HLX14: 5.9% vs. Prolia/HLX14: 9.1% vs. Prolia/Prolia: 8.2%). The most common PT in treatment related AEs reported in the Prolia/HLX14 group was hypercholesterolaemia (HLX14/HLX14: 0.9% vs. Prolia/HLX14: 2.7% vs. Prolia/Prolia: 0%). However, total numbers of patients with the respective events appear low and do not give rise to concern. Furthermore, rates in AESIs, including hypersensitivity reactions (HLX14/HLX14: 1.8%, Prolia/HLX14: 0.9%, Prolia/Prolia: 3.6%), and serious AEs (HLX14/HLX14: 2.7%, Prolia/HLX14: 0.9%, Prolia/Prolia: 5.5%) were lower in the study group that has switched treatments Treatment-related AESIs were reported in only 0.9% of patients in each study group, but no treatment-related SAE was reported. Fractures were reported for one subject in each study group, but no subjects died during the treatment period 2.

In conclusion, no critical imbalance in the reported safety profile was identified for this study group compared to the other two study groups that have maintained the treatment from period 1.

Drug-drug interaction, Special population and post-marketing experience

No drug interaction studies or safety studies focused on the special population were performed. No post-marketing data is available. This is acceptable for biosimilars.

Immunogenicity related to Safety

It is acknowledged that no positive ADA samples were observed for any subject in part I of study HLX14-001. During study HLX14-001 part II, the rate of subjects that have developed ADAs while on treatment with any of the study drugs was lower when treated with HLX14 compared to Prolia (10.3% and 20.6%, respectively) and study HLX14-002-PMOP301 (10.9% and 13.6%, respectively). The rate of NAbs was very low and only subjects treated with Prolia were detected with NAbs (n=1 treated with US-Prolia in study HLX14-001 and n=2 treated with EU-Prolia in study HLX14-002-PMOP301). The imbalance observed in study HLX14-001 appears acceptable, as the observed lower incidence of ADAs and NAbs during treatment with HLX14 compared to Prolia does not elicit concerns for the treatment with HLX14. With respect to adverse events reported for ADA-positive subjects during the study, no concern arises when comparing the rate and character of safety events in ADA-positive patients treated with HLX14 or Prolia, or when comparing the rate and character of safety events in ADA-positive subjects to those in ADA-negative subjects within the same or across treatment arms. Of note, the number of patients with ADAs is generally low, which compromises the interpretation of subject proportions with safety event in this subgroup. The only denosumab-related AE of grade ≥3 in an ADA-positive subject was the PT blood triglycerides increase in a healthy subject treated with HLX14 in part II of study HLX14-001. However, the same PT of grade ≥3 also occurred in 2 ADA-negative subjects treated with Prolia in the same study. Serious AEs in ADA-positive subjects only occurred in patients treated with Prolia during study HLX14-002-PMOP301 (PTs Coronary artery disease and lumbar vertebral fracture). However, similar events also occurred in subjects treated with HLX14 in ADA-negative subjects. Thus, grade ≥3 and serious events reported in ADA positive subjects do not appear specifically related to the ADA status. As reported above, AESIs occurred in a mildly higher rate in subjects treated with Prolia compared to subjects treated with HLX14 (in both clinical studies), which is also reflected in the rate of ADA-positive subjects with event of special interest (0 vs. 11.4% in study HLX14-001 and 3.6% vs. 8.6% in study HLX14-002-PMOP301 in HLX14 and Prolia, respectively). All

events were PTs hypocalcaemia or blood calcium decreased (only in study HLX14-001), which both also occurred in ADA-negative subjects in a comparable ratio. Thus, no relation to ADA status is assumed for grade ≥3 events, AESIs or serious events. In conclusion, results on the influence of immunogenicity on safety events do support the proposed conclusion on biosimilarity between HLX14 and Prolia.

2.5.10. Conclusions on the clinical safety

Based on the provided data of two clinical studies, one in healthy male volunteers and one in female PMO patients, no unexpected safety concerns were detected across the clinical studies. The observed safety findings correspond to the known safety profile of the reference product Prolia and were well balanced between treatment groups. Also, the rate of fractures as TEAE, Grade ≥3 or serious event were balanced between both treatment groups of study HLX14-002-PMOP301 in postmenopausal women with osteoporosis at high risk of fracture. Treatment switch from the originator Prolia to HLX14 also does not seem to be associated to any critical safety concerns.

Overall, the collected safety data appears indicative of comparable safety between the biosimilar candidate HLX14 and the RMP Prolia.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table: *Summary of safety concerns*

Table 48. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumour of bone • Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing information	• Use in patients with prior intravenous bisphosphonate treatment

Summary of safety concerns	
	• Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone • Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Table 49. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk - Osteonecrosis of the jaw	Routine risk minimisation measures: • SmPC Section 4.3 • SmPC Section 4.4, where recommendations for oral examination, maintenance of good oral hygiene, management of patients with unavoidable invasive dental procedure, and temporary interruption are discussed. • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 2, where recommendations for oral examination, maintenance of good oral hygiene, management of patients with unavoidable invasive dental procedure, and sign of ONJ are discussed. • PIL Section 4, where symptoms of ONJ is discussed. • Prescription only. Additional risk minimisation measures: • Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Important Identified Risk - Atypical femoral fracture	Routine risk minimisation measures: • SmPC Section 4.4, where recommendations for reporting new or unusual thigh, hip, or groin pain are discussed.	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• SmPC Section 4.8 • PIL Section 2, where recommendations for reporting new or unusual thigh, hip, or groin pain is discussed. • PIL Section 4, where signs of thigh bone fracture are discussed. • Prescription only. Additional risk minimisation measures: • None	reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Important Identified Risk - Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	Routine risk minimisation measures: • SmPC Section 4.4, where recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of Bilprevda are discussed. • SmPC Section 4.8 • PIL Section 2, where recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of Bilprevda treatment are discussed. • PIL Section 4 • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important Potential Risk - Cardiovascular events	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important Potential Risk - Malignancy	Routine risk minimisation measures: • SmPC Section 4.4, where recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis are discussed. • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 4 • Prescription only.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: • None	
Important Potential Risk - Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important Potential Risk - Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Missing Information – Use in patients with prior intravenous treatment with bisphosphonate treatment	Routine risk minimisation measures: • SmPC Section 4.5 • SmPC Section 5.1 • PIL Section 2 • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Missing Information - Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Missing Information - Off-label use in patients with giant cell tumour of bone that is resectable where resection is	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
unlikely to result in severe morbidity		reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.2 is acceptable.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Prolia. The bridging report submitted by the applicant has been found acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Bilprevda (denosumab) is included in the additional monitoring list as it is a biological product.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Bilprevda was developed as a biosimilar product to Xgeva (INN: denosumab), marketed by Amgen and was developed with the same strength and presentation (Xgeva: 120 mg/1.7mL single use vial). Xgeva is indicated for:

- The prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone (see section 5.1).
- The treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

The applicant intends to claim all of the authorized indications of the reference product.

Analytical biosimilarity exercise

In general, a sound and well-established biosimilarity evaluation was performed. HLX14 with the active substance denosumab developed as a biosimilar medicinal product against both EU approved RMPs, Prolia and Xgeva. HLX14 was developed in three presentations, HLX14 (60 mg, vial) and HLX14 (60 mg, PFS) as biosimilar to Prolia with the same components and composition, and HLX14 (120 mg, vial) as biosimilar to XGEVA with the same components and composition. In the analytical similarity assessment, both RMPs, Prolia and Xgeva were grouped together to establish analytical similarity acceptance criteria. Furthermore, for quality attributes which are not impacted by DP manufacturing process or container closure system the analytical results of HLX14 products from all three different presentations were grouped together in the statistical analysis for comparing HLX14 with the reference medicinal products (RMPs) for demonstrating the analytical similarity between HLX14 and RMPs. To address demonstrate comparability of the three HLX14 presentations, the applicant performed a comprehensive comparability evaluation of the three HLX14 presentations via a 3-way comparability study conducted per ICH Q5E.

Summary of Clinical Data

The applicant has developed one presentation of HLX14 as the proposed biosimilar of Xgeva: HLX14 120 mg in single use vial, administered subcutaneously. Analytical similarity studies were performed against the reference products, Prolia and Xgeva, and clinical studies were performed against the reference product, Prolia. The clinical programme consists of two clinical studies: a Phase I study (HLX14-001) and a Phase III study (HLX14-002-PMOP301).

- HLX14-001 was a randomized, parallel, single-dose, subcutaneous injection, Phase I clinical study of HLX14 versus Prolia (Denosumab) in Chinese Healthy Adult Male Subjects for Comparison in Pharmacokinetic Characteristics, Safety, and Immunogenicity consisting of two parts. The primary objective for part I was to compare the PK parameters of HLX14 and EU-Prolia to further provide basis for the study design of part II, and the primary objective for part II was to compare the PK similarity of HLX14 and Prolia (US, EU, and CN-sourced denosumab). Secondary objectives included comparison of PD, safety, tolerability, and immunogenicity.

- HLX14-002-PMOP301 was a randomized, double-blind, international multicentre, parallel-controlled phase III clinical study to compare the efficacy, PD, PK, immunogenicity, and safety of HLX14 versus Prolia (EU-sourced) injection in postmenopausal women with osteoporosis at high risk of fracture. Subjects were randomized in a 1:1 ratio for the main treatment period (52 weeks). A treatment transition from Prolia to HLX14 was investigated in a subpopulation from weeks 52-78.

To meet regulatory requirements, and optimize the trial design, the applicant sought EMA Scientific Advice twice. Recommendations given by the CHMP were largely adopted.

3.2. Results supporting biosimilarity

Quality

The results from the similarity exercise principally support the biosimilarity claim. For most quality attributes similarity could be shown. For a few quality attributes differences were observed but appropriately justified. A comparable degradation under various stress conditions as well as the results from the study comparative accelerated stability further support the comparability claim. Finally, all analytical methods used for the similarity assessment were validated or qualified for the intended use.

Clinical

PK/PD

Study HLX14-001

The GMRs for primary PK parameters of HLX14 compared to EU-Prolia were 0.97 (0.91, 1.04), 0.98 (0.91, 1.05) and 0.99 (0.93, 1.06) for AUC0-inf, AUC0-t and Cmax, respectively. Similarity in these parameters was also demonstrated for all other pairings of HLX14, EU-Prolia, US-Prolia and CN-Prolia, with the range of 90% CIs for GMR ranging from 0.90 to 1.17. Two sensitivity analyses were performed to support the results of the primary analysis. Secondary PK parameters were T_{max}, CL/F, λz, t1/2, Vd/F, and %AUCex, $AUC_{0\text{-}28d}$, and $AUC_{0\text{-}112d}$ all of which were overall comparable between the treatment groups. Although the PK assay had a relatively high LLOQ, the %AUC extrapolated is considered low for all treatment groups at 3.146%, 3.535%, 3.814%, and 3.703% for HLX14, US, EU, CN-Prolia respectively.

C-telopeptide of type I collagen measured via serum (s-CTX) was measured as PD parameter, with corresponding PD endpoints being presented using descriptive statistics. Concentration time-graphs, descriptive statistics as well as statistical analysis did not show any difference between the study groups. The GMRs for AUEC0-t and Imax in part II were similar for all treatment pairs and the 95% CIs were entirely contained within the acceptance limits of 80% to 125% (range: 89% to 116%).

Study HLX14-002-PMOP301

s-CTX and P1NP were evaluated for PD analysis of HLX14 compared with EU-Prolia. Baseline values for s-CTX concentration were similar between HLX 14 and EU-Prolia (0.493 ng/ml [SD: 0.2207] for HLX14 and 0.501 ng/ml [SD: 0.2269] for EU-Prolia; ITT set). The primary analysis of $AUEC_{0\text{-}26W}$ for s-CTX comparing HLX14 against EU-Prolia showed a geometric LS mean ratio of 1.01 (95% CI: 0.98, 1.05), which is considered supportive of biosimilarity as it falls within the pre-specified equivalence margins. The results of the primary analysis are supported by the results of the sensitivity analyses as well as those of the secondary s-CTX endpoint, which showed similarity at all measured time points. The PK profiles for the HLX14 and Prolia were similar throughout the study period.

Efficacy

Study HLX14-002-PMOP301

Equivalence was demonstrated in both co-primary endpoints in postmenopausal women with osteoporosis at high risk of fracture. The LS mean difference percent change from baseline in bone mineral density between the HLX14 and Prolia groups was 0.21% (95% CI: -0.51%, 0.94%). This met pre-defined equivalence criteria (±1.45%). The applicant conducted several sensitivity analyses that further support the robustness of the primary conclusions.

The results of the co-primary endpoints are supported by those of the secondary endpoints: fracture rate from baseline to week 52, week 78, %cfb to week 26, 78 in BMD at lumbar spine, %cfb to week 52, 78 in BMD at total hip, as well as %cfb to week 52, week 78 in BMD at the femoral neck. Similar results were observed in all secondary endpoints in the HLX14 and Prolia study groups. The applicant provided sensitivity analyses for all endpoints to support the robustness of the results.

Safety

Study HLX14-001 and Study HLX14-002-PMOP301

Based on the provided data of two clinical studies, one in healthy male volunteers and one in female PMO patients, no unexpected safety concerns were detected across the clinical studies. The observed safety findings correspond to the known safety profile of the reference product Prolia and were well balanced between treatment groups. Also, the rate of fractures as TEAE, Grade ≥3 or serious event were balanced between both treatment groups of study HLX14-002-PMOP301 in postmenopausal women with osteoporosis at high risk of fracture. Overall, the collected safety data appears indicative of comparable safety between the biosimilar candidate HLX14 and the RMP Prolia.

Immunogenicity

Study HLX14-001

Results on the influence of immunogenicity on safety events do support the proposed conclusion on biosimilarity between HLX14 and Prolia.

Study HLX14-002-PMOP301

Results on the influence of immunogenicity on safety events do support the proposed conclusion on biosimilarity between HLX14 and Prolia.

3.3. Uncertainties and limitations about biosimilarity

Quality

No uncertainties addressing the biosimilarity claim are left.

Clinical

2 subjects in study HLX14-001, and 4 subjects in study HLX14-002-PMOP301 had measurable serum denosumab concentrations at D1 pre-dose. Although subjects had not been previously exposed to the study drug, it is unclear why measurable concentrations of denosumab were measured, and the finding could not be satisfactorily explained.

3.4. Discussion on biosimilarity

Quality

The applicant's conclusion that biosimilarity has been sufficiently demonstrated, can be agreed.

Clinical

The applicant conducted two clinical trials to support the biosimilarity of HLX14 and Prolia: HLX14-001, a phase I trial in healthy volunteers to compare the PK, PD, safety and immunogenicity of HLX 14 against EU, US, and CN-Prolia, as well as phase III HLX14-002-PMOP301. No concerns arise based on critical study design aspects and both studies are generally considered to be able to detect a difference between the IPs.

In study HLX14-001, PK similarity was demonstrated in healthy male volunteers in the primary endpoints (AUC0-inf, AUC0-t, & Cmax), as well as all secondary endpoints. The sampling frequency and the chosen endpoints are considered acceptable to determine PK similarity between the IPs. In study HLX14-002-PMOP301 comparable serum denosumab concentrations were measured at all time points, although the sampling schedule was more sparse compared to the phase I trial. These overall positive findings are contrasted by a finding, where in both trials (2 in HLX14-001, 6 in HLX14-002-PMOP301) subjects had measurable denosumab concentrations at D1 pre-administration.

PD similarity was assessed in both trials. In the phase I, as well as the phase III trial, concentration time-graphs and descriptive statistics did not show any difference between the study groups. The GMRs for AUEC0-t, Imin, and Imax in part II of study HLX14-001 were similar for all treatment pairs and the 95% CIs were entirely contained within the acceptance limits of 80% to 125% (range: 81% to 116%). Imin was also comparable between the treatment groups. In study HLX14-002-PMOP301, the concentration time-graphs for s-CTX and P1NP were largely overlapping.

The PK and PD results of the provided studies support biosimilarity between test and reference product HLX14 and Prolia.

From an efficacy perspective, the primary analysis based on the %CfB in LS-BMD at Week 52 was met as the 95% CI of the difference between the HLX14 and the US-Prolia group was within the pre-specified equivalence margins (-1.45%, 1.45%). The co-primary PD endpoint (AUEC of s-CTX over the initial 6 months) was met, and similarity was further confirmed by secondary endpoints results. Thus, the provided efficacy data support the biosimilarity of HLX14 and US-Prolia.

No unexpected safety concerns were detected across the clinical studies. The observed safety findings correspond to the known safety profile of the reference product Prolia and were well balanced between treatment groups. Also, the rate of fractures as TEAE, Grade ≥3 or serious event were balanced between both treatment groups of study HLX14-002-PMOP301 in postmenopausal women with osteoporosis at high risk of fracture.

3.5. Extrapolation of safety and efficacy

HLX14 was developed as a biosimilar to Prolia and Xgeva, sharing the same mechanism of action. The monoclonal antibody denosumab targets and binds to RANKL, preventing its interaction with RANK. This inhibition reduces osteoclast formation and function, thereby decreasing bone resorption and cancer-induced bone destruction. Phase III Study HLX14-002-PMOP301 was conducted in postmenopausal women with osteoporosis (PMO). For all indications of Prolia and Xgeva, the mechanism of action of denosumab is identical, i.e. binding to RANK-L and thus preventing activation of its receptor RANK. Consequently, the efficacy results can be extrapolated to all therapeutic indications of Prolia and Xgeva approved in the EU. The treatment population is considered relevant and sensitive enough for the biosimilarity assessment.

This extrapolation is further supported by comparable biological characteristics, demonstrated by a broad panel of binding and cell-based bioassays, pharmacokinetic (PK), safety, and immunogenicity profiles of denosumab across different indications and patient populations, as summarized in the product information for Prolia/Xgeva.

Clinical data was generated in healthy volunteers and female post-menopausal osteoporosis patients. Both populations are considered sensitive in terms of evaluating biosimilarity. Therefore, the safety and efficacy profile of HLX14, as assessed in the post-menopausal osteoporosis (PMO) indication, can be extrapolated to all indications applied for HLX14.

The majority of subjects enrolled in both studies are Asian. Within the scientific advice, the applicant was asked to include a discussion on ethic issues supporting the study data extrapolation between different ethnic groups (EU population vs non-EU population). The comprehensive justification discussed the published studies, PI and the globally approved clinical use of the reference medicinal product, dietary factors, physical activity, sun exposure, medical practice etc. The applicant states that the data and evidence presented support that the results/findings observed between the reference product Prolia and HLX14 in an Asian population and can be reasonably generalized to a non-Asian population. This is considered acceptable from the safety point of view.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Bilprevda is considered biosimilar to Xgeva. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Bilprevda is favourable in the following indication(s):

> Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone (see section 5.1).
>
> Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set

out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that a patient reminder card regarding osteonecrosis of the jaw is implemented.