12 December 2024
EMA/51220/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Osenvelt

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/006157/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
$AUC_{0\text{-}168hr}$	Area under the serum concentration-time curve from 0 to 168 hours
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-}last}$	Area under the concentration-time curve from time zero to the last quantifiable concentration
AUEC	Area under the effect curve
BMD	Bone mineral density
BMI	Body max index
BPD	Biological product development
CELISA	Cellular enzyme linked immunosorbent assay
CHO	Chinese hamster ovary (cell line)
CI	Confidence interval
C_{max}	Maximum observed serum concentration
CMC	Chemistry, manufacturing and control
COVID-19	Coronavirus disease of 2019
CRO	Clinical research organisation
CSR	Clinical study report
CT-P41	Osenvelt
C_{trough}	Trough serum concentration
CTX-1	Type 1 collagen telopeptide C
DRM	Data review meeting
DSMB	Data safety monitoring board
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECLA	Electrochemiluminescence assay
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicine Agency
EOS	End-of-study
EQ-5D-5L	EuroQoL-5 dimensions-5 levels health survey
EU	European Union
FAS	Full analysis set
FcRn	Neonatal Fc receptor
FcγRIIa	Fc-gamma receptor IIa
FcγRIIIa	Fc-gamma receptor IIIa
FDA	Food and drug administration
GCP	Good clinical practice
GLP	Good laboratory practise
HF	Human factor study
ICH	International Council for Harmonisation
IgG	Immunoglobulin G

IND	Investigational new drug
INN	International non-proprietary name
ISI	Integrated summary of immunogenicity
LLoQ	Lower limit of quantification
LS	Least squares
MAA	Marketing authorisation application
mAb	Monoclonal antibody
MAR	Missing at random
MNAR	Missing not at random
MSD	Meso scale discovery
NAb	Neutralising antibody
NI	Non-inferiority
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
ONJ	Osteonecrosis of jaw
OPAQ-SV	Osteoporosis assessment questionnaire-short version
OPG	Osteoprotegerin
P1NP	Procollagen type 1 N-terminal propeptide
PD	Pharmacodynamic
PFS	Pre-filled syringe
PFS-S	Pre-filled syringe (with safety guard)
PK	Pharmacokinetic
PMO	Postmenopausal women with osteoporosis
PPS	Per-protocol set
PT	Preferred term
RANK	Receptor activator of nuclear factor kappa-B
RANKL	Receptor activator of nuclear factor kappa-B ligand
RMP	Reference medicinal product
SAE	Serious adverse event
SC	Subcutaneous
s-CTX	Serum type 1 C-telopeptide
SD	Standard deviation
SE	Standard error
SEC-HPLC-UV	Size exclusion chromatography High-Performance Liquid Chromatography-Ultraviolet
SmPC	Summary of product characteristics
SOC	System organ class
SPA	Special protocol assessment
SPR	Surface plasmon resonance
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
TESAE	Treatment-emergent serious adverse event
TK	Toxicokinetic
ULoQ	Upper limit of quantification
US	United States
USPI	United States prescribing information
UV-SPEC	UV spectrophotometric

VAS	Visual analogue scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celltrion Healthcare Hungary Kft. submitted on 8 March 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Osenvelt, 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

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.

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 in via
- Marketing authorisation holder: Amgen Europe B.V.; Minervum 7061; 4817 ZK Breda; The Netherlands
- 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 in via
- Marketing authorisation holder: Amgen Europe B.V.; Minervum 7061; 4817 ZK Breda; The Netherlands
- 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 comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: XGEVA 120 mg solution for injection in via
- Marketing authorisation holder: Amgen Europe B.V.; Minervum 7061; 4817 ZK Breda; The Netherlands
- Date of authorisation: 13-07-2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: 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**
January 2020	EMEA/H/SA/4399/1/2020/III	*Adriana Andric, Elena Wolff-Holz, Sheila Killalea*
September 2020	EMEA/H/SA/4399/1/FU/1/2020/II	*Elena Wolff-Holz, Juha Kolehmainen*
February 2021	EMEA/SA/0000050271	*Andrea Laslop, Elina Rönnemaa*

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

- EMEA/H/SA/4399/1/2020/III

Physicochemical and functional tests to demonstrate similarity of CT-P41 to EU-approved Prolia and EU-approved Xgeva; the proposed release and long-term stability test items for CT-P41 drug substance and drug products; the need for additional human factor and usability studies.

Design of Phase I and Phase III clinical studies including the reference product, the study populations, the primary and secondary endpoints, the equivalence margin, sample size and power, and the duration of the studies; the requirements for the extrapolation of clinical data to all indications currently approved for Prolia and Xgeva.

- EMEA/H/SA/4399/1/FU/1/2020/II

Design of a Phase I PK study CT-P41 1.2 with emphasis on the dose to use.

Design of a Phase III comparative study of CT-P41 and US-licensed Prolia including stratification factors, inclusion/exclusion criteria, primary pharmacodynamics analysis (including equivalence margin and analysis set), primary efficacy analysis (including equivalence margin and analysis set), and single transition; marketing authorisation application data submission strategy.

- EMA/SA/0000050271

Acceptability of the proposed time point upon which additional secondary endpoints for PK similarity are to be assessed.

Design of a Phase III comparative efficacy study with a focus on primary pharmacodynamics analysis and primary efficacy analysis.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Christian Gartner

The application was received by the EMA on	8 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	17 June 2024
The CHMP Co-Rapporteur's Critique was circulated to all CHMP and PRAC members on	1 July 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	1 July 2024
The PRAC Rapporteur's updated assessment report was circulated to all PRAC and CHMP members on	10 July 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	25 July 2024
The applicant submitted the responses to the CHMP consolidated list of questions on	13 September 2024
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	21 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint updated assessment report on the responses to the list of questions to all CHMP and PRAC members on	7 November 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	14 November 2024
The applicant submitted the responses to the CHMP list of outstanding issues on	19 November 2024

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	27 November 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint updated assessment report on the responses to the list of questions to all CHMP and PRAC members on	5 December 2024
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 Osenvelt on	12 December 2024

2. Scientific discussion

2.1. About the product

Osenvelt 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 solution (70 mg/mL) for injection in vial

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

2.2. Type of Application and aspects on development

During the development of CT-P41, the applicant sought scientific advice from the EMA Scientific Advice Working Party (SAWP) three times. These centralised advices covered all the areas of development. All aspects that were discussed critically during these advice procedures and are deviating from the final study designs are discussed in the respective methods or result sections.

2.3. Quality aspects

2.3.1. Introduction

Osenvelt was developed as a biosimilar product to Xgeva. Osenvelt finished product (FP) is presented as a sterile solution for injection for subcutaneous use in a single dose vial, containing 120 mg (70 mg/mL) of denosumab as active substance (AS).

Other ingredients are: acetic acid, sodium acetate trihydrate, sorbitol (E420), polysorbate 20 (E432) and water for injections.

Osenvelt is available in a single use type 1 glass vial and is supplied in pack sizes of one, three or four vials.

2.3.2. Active Substance

2.3.2.1. General information

Denosumab (CT-P41) is a human monoclonal immunoglobulin G2 (IgG2) produced in a Chinese Hamster Ovary (CHO) cell line using recombinant DNA technology. Like other IgG, CT-P41 is a glycoprotein with one N-linked glycosylation site (Asn298) in the CH2 domain of each heavy chain. The detected oligosaccharides are mostly G0F and G1F structures.

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

2.3.2.2. Manufacture, characterisation and process controls

Manufacturers

Name, address, and responsibilities of all manufacturers involved in manufacture and in-process control (IPC), quality control, and stability testing of CT-P41 active substance as well as manufacturing and storage sites of cell banks are listed.

All active substance manufacturing sites hold valid proof of GMP compliance.

Description of manufacturing process and process controls

The CT-P41 AS for commercial supply is manufactured using a production bioreactor expanded from the current working cell bank (WCB). The process set-up is a standard monoclonal platform technology and consists of an upstream and downstream process.

The upstream process consists of several cell expansion steps, harvest and finally filtration. In the downstream process the clarified harvest is purified using a series of purification steps. Purification includes virus inactivation and virus removal steps. Finally, the CT-P41 active substance is filtered into bottles and stored.

In general, all steps are adequately described and flow-charts with process controls are provided, including critical input process parameters and critical in-process tests.

Control of materials

Information on the source of the cell substrate and analysis of the expression construct to develop the Master Cell Bank (MCB) is described in satisfactory detail. Chinese hamster cells (CHO) were used to generate the transfected cell line. The limit of in vitro cell age (LIVCA) for CT-P41 production was evaluated. Results for LIVCA studies have been presented for identity and purity as well as for genetic stability. Stability analysis of the production clone is considered adequately performed.

A common two-tiered cell banking system consisting of a Master Cell Bank (MCB) and Working Cell Bank (WCB), using the Pre-MCB, is used. Cell banks (MCB, WCB, EPCB) are tested for identity, purity and genetic characterisation/stability. Protocol for the establishment of future WCB has been described and is considered satisfactory.

In addition, the End of Product Cell Bank (EPCB) was characterised for identity, purity and genetic stability. It can be agreed with the applicant´s conclusion, that continued cell culture beyond routine manufacturing conditions is acceptable from a quality perspective.

Overall, the cell banking system, characterisation and testing are adequately described.

Raw materials used for the manufacture of AS are adequately presented. The information provided is adequate and sufficient.

Control of critical steps and intermediates

Overall, the approach to define criticality of parameters and in-process tests is in line with relevant EMA guidelines. The control strategy was developed by establishing quality target product profile (QTPP) for CT-P41 and critical quality attributes (CQAs). The provided level of information on CQAs including the proposed control strategy is considered acceptable. A critical process parameter (CPP) is defined as a process parameter that could affect CQAs.

Overall, the presented process controls and in-process tests for AS manufacturing are considered appropriate.

Process validation

Process validation for CT-P41 active substance was carried out at commercial scale at CELLTRION Plant II (CLT2), Incheon, Republic of Korea, the intended production site for the AS.

Overall, there were no batch failure during validation, and all batches met the active substance specifications. Based on the process validation data, it can be concluded that the process consistency has been demonstrated by the process parameters and controls meeting their requirements.

Impurity clearance studies were performed. Sufficient clearance of process related impurities was demonstrated. The impurity clearance is supported by the in-process testing results during the process validation studies confirming adequate removal of impurities. Descriptions of the analytical methods used for the impurity detection are presented in the dossier.

Manufacturing process development

Manufacturing process development has been described and summarised. Description of changes and reasons for changes (justification) with respect to the impact on quality have been provided and acceptable. Comparability of the different process versions has been addressed, and the data demonstrated comparability of denosumab active substance originating from clinical and process validation batches.

Characterisation

Characterisation studies were performed using several batches of CT-P41 active substance and several batches of CT-P41 finished product. All batches used in the characterisation studies are commercial/PV batches. All testing was performed in a side-by-side manner to allow direct comparison of the data from AS and FP. Orthogonal methodologies were used to elucidate the primary and higher order structures, as well as the charged variants, glycan structures, purity, content and impurities. Details of the analytical methods and their qualification have been provided.

The primary sequence was confirmed. The expected peptides were identified, and the molecular weights of the peptides were matching with their corresponding theoretical molecular weights. The amino acid sequence has been additionally confirmed.

Expected molecular mass for the intact protein was confirmed. Confirmation on the higher order structure was achieved.

Further characterisation of charged variants has been included. Charge variants of AS and FP samples were comparable and consistent.

Overall, the performed characterisation studies are considered relevant and cover a wide variety of physicochemical and biological characterisation studies. Additionally, based on the provided data the AS and FP are comparable on quality, indicating that the finished product manufacturing process do not compromise the physicochemical quality or biological activities of the final product.

Impurities

Product-related impurities/substances as well as process-related impurities have been identified. Impurities are characterised and their biological activities (product-related impurities) and safety aspects are discussed.

Evaluation concerning nitrosamines has been provided. The applicant´s conclusions on the potential risk of nitrosamines being negligible, is agreed.

2.3.2.3. Specification

Specifications

The specification for the active substance includes compendial tests and non-compendial tests. The proposed panel of release tests cover identity, quantity, purity/impurity, potency, general tests, charge heterogeneity, glycosylation and safety. In general, the panel of tests are in line with ICH Q6B and are considered appropriate for routine control of a monoclonal antibody at release.

Justification of specification

The proposed acceptance criteria for AS release and stability are adequately justified and acceptable. Aspects on historical data, analytical and manufacturing variability, regulatory guidelines, pharmacopoeial limits and published literature have been taken into account, when establishing the specification limits. The proposed end-of-shelf-life specification is identical to the proposed commercial specification for release except for the omission of some tests for attributes that not expected to change over time.

Analytical methods

Analytical methods have been adequately described.

Compendial analytical methods are performed in accordance with the relevant Ph. Eur. monographs. The non-compendial method descriptions are sufficiently detailed and include details regarding equipment, reagents, operating conditions, sample and standard preparation, assay controls and system of suitability.

The analytical procedures have been appropriately validated in accordance with ICH Q2(R1). Verification data has been presented for all the compendial methods and the data presented shows that all the verification results met the acceptance criteria, and the methods are considered appropriate for their intended use.

Batch analysis

Batch analysis data is presented for several AS batches. All results comply with the specifications valid at time of testing and comply with the proposed commercial specifications. The presented results demonstrate that the manufacturing process reliably delivers AS with consistent and acceptable quality.

Reference standards

Overall, the history of reference standards used during the product development to batch release have been adequately described.

A two-tiered reference standard system is used for commercial manufacturing including primary reference standard (PRS) and working reference standards (WRS). The WRS is used for routine lot release and stability testing, comparability study and assay method development/validation.

The PRS and WRS standards have been tested according to extensive testing according to the pre-defined specification in place at the time and additional characterisation testing. Qualification data demonstrated suitability of the PRS and WRS. PRS and WRS are re-qualified in line with a pre-defined stability protocol. Re-qualification acceptance criteria for PRS and WRS are acceptable.

New WRS will be qualified against the PRS. The proposed protocol for qualification of new WRS is acceptable. The information provided on reference standards is sufficient.

Container closure system (CCS)

CT-P41 active substance is filled into pre-sterilised, pyrogen free bottles. Leachable studies are performed for the container closure system. Specifications for the CCS are listed in the dossier.

According to the photostability studies, the AS is photo-sensitive and should be protected from light. Each container is labelled to indicate that the contents should be protected from light. The container closure integrity test was performed. Leachable studies were performed. No elements or compounds were detected above the analytical evaluation threshold (AET) in the active substance samples. Based on the provided results so far, no safety risk is expected in the product. The information provided is adequate and sufficient.

2.3.2.4. Stability

Stability studies have been performed in accordance with ICH guidelines in terms of testing frequency and storage conditions using validated methods.

The shelf-life claimed for the CT-P41 AS stored at long-term condition was proposed based on the long-term, intermediate, accelerated and stressed stability data of the clinical batches. Considering the stability data, the comparability data provided and the manufacturing process being identical between the clinical and the commercial batches, the proposed shelf-life is considered acceptable.

For photostability studies, the available data indicate that slight changes can be observed in purity for AS without coverage. Thus, the active substance should be stored away from sources of light, during both storage and shipment. Specifically, the CT-P41 active substance is stored in a dark freezer or refrigerator (without glass doors).

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product of CT-P41 is a sterile, preservative free solution for injection available in a vial presentation and intended for subcutaneous administration.

Each vial is designed to deliver a single dose of 120 mg CT-P41 active substance in a 1.7 mL of solution at a nominal concentration of 70.0 mg/mL. Other ingredients are: acetic acid, sodium acetate trihydrate, sorbitol (E420), polysorbate 20 (E432) and water for injections.

No formula overages are included. The overfill ensuring the respective nominal volume of the finished product is included and is considered acceptable.

The qualitative and quantitative composition of CT-P41 FP in a single vial along with the function and grade of excipients have been provided.

The finished CT-P41 FP was developed to have the same formulation, route of administration and product strength as the reference product, EU-Xgeva. All the excipients used in the FP comply with Ph. Eur. requirements and are commonly used in the manufacturing of parenteral pharmaceutical preparations. No novel excipients nor excipients originated from human or animal sources are used.

The container closure system used in formulation development studies was same as that intended for commercial supply. Overall, sufficient formulation development studies were conducted and the conclusions drawn by the applicant can be agreed. Most importantly, the results clearly indicate that the formulation is suitable and robust.

The manufacturing process development history of FP from early developmental to the proposed commercial process has been provided. In general, the changes in the manufacturing processes are minor mainly relating to scale-up and modifications in IPC limits due to equipment differences between the manufacturing sites.

Analytical comparability of the manufacturing processes was demonstrated in accordance with ICH Q5E. Batch release and extended characterisation data were used to demonstrate the comparability.

Comparison between CT-P41 FP presentations did not reveal any significant differences in the quality attributes that would have an adverse impact on safety or efficacy. This demonstrates that the difference in formulation and manufacturing process of CT-P41 PFS and vial FP presentations has no impact on product quality.

2.3.3.2. Manufacture of the product and process controls

Sites responsible for the manufacture, testing and release of the finished product are provided. All finished product manufacturing sites hold valid proof of EU-GMP compliance.

The manufacturing process of the finished product is a standard manufacturing process which comprises AS mixing, filtration, aseptic filling, stoppering, and capping. Then, the vials are visually inspected and stored at 2-8°C at the manufacturing site.

A narrative description of the full manufacturing process was provided, accompanied by a flow chart describing each step of the process including process parameters with operating ranges and in-process controls with proposed acceptance criterion. Overall, the manufacturing process description was adequately justified by the manufacturing development and validation data.

The quality target product profile (QTPP) for CT-P41 was developed in line with ICH Q8 guideline including the following considerations: the intended use in clinical setting, route of administration, dosage form, physical, chemical, biological or microbiological properties, dosage strength, container closure system, sterility, purity and stability.

Critical quality attributes (CQAs) relevant to CT-P41 were established using a combination of risk assessment and data from early development and product characterisation studies as well as experience from commercial scale manufacturing and analytical similarity studies between CT-P41 and reference product.

The manufacturing process of CT-P41 FP is controlled by operating (input) and testing (output) parameters with acceptable ranges. Critical process parameters (CPPs) with their proposed limits/ranges together with appropriate justifications were presented in tables for all relevant manufacturing steps.

Overall, the presented process controls seem appropriate and the proposed control strategy for the FP manufacturing process can be agreed.

Process validation

The FP manufacturing process was validated by producing several commercial scale PPQ lots at the proposed commercial manufacturing site. Each PPQ lot was manufactured from AS originating from different AS lots. This is acknowledged.

Overall, all PPQ batches were successfully validated, the presented data met acceptance criteria, demonstrating consistency and reliability of the FP manufacturing processes. All batches met the release results of the proposed commercial specification acceptance criteria.

Adequate data of filter validation was presented, and it is considered acceptable. These studies demonstrated that no leachables are present, the formulation does not compromise the integrity of the filters, and the filters have an adequate bacterial retention capability.

The proposed hold and processing times for commercial manufacturing process are clearly presented and summarised. The hold times have been adequately justified and validated.

The primary packaging components of CT-P41 FP includes vials and stoppers which are sterilised prior to introduction into the manufacturing process. Sterilisation methods and supporting validation data for product-contact materials are sufficiently described.

2.3.3.3. Product specification

The CT-P41 FP specifications cover all relevant characteristics and are set in accordance with ICH Q6B principles and according to Ph. Eur. requirements. Comprehensive panel of release specifications includes tests for identity, potency, purity and impurities, microbiological quality, content and general properties.

Overall, the proposed CT-P41 FP specifications and their acceptance limits are considered appropriate and in line with the current guidance.

The risk assessment regarding nitrosamine impurities conducted was designed to evaluate all potential sources of nitrosamine formation or contamination during manufacture of the FP. No significant risk of nitrosamine impurities was identified, is agreed.

The risk assessment and evaluation of elemental impurities in accordance with ICH Q3D has been provided. The elemental impurity study demonstrated an extremely low risk from elemental impurities.

Analytical procedures

The analytical procedures used in the specification determination of the finished FP of CT-P41 included both compendial and non-compendial methods. Compendial methods are based on respective Ph. Eur. monographs. The verification data for all compendial methods are presented and methods are considered suitable for their intended use.

Non-compendial analytical methods for the finished FP of CT-P41 are originally fully validated.

In general, the validation of non-compendial analytical procedures has been done according to relevant guidelines. The methods validation information provided is adequate and sufficient.

Batch analysis

Batch analytical data was provided for several FP batches from development and commercial manufacturing processes. All batches met the acceptance criteria of release in place at the time indicating adequate batch-to-batch consistency and controlled FP manufacturing process.

Container closure

The primary packaging materials of the finished FP of CT-P41 consist of Type I glass vial, 3 mL, rubber stopper and flip-off seal.

The vial and stopper are of Ph. Eur. quality. Certificate of analysis of the components of the container closure system was provided. Also, specifications for primary and secondary container closure systems were provided.

2.3.3.4. Stability of the product

A shelf-life of 3 years is claimed for the CT-P41 FP when stored at the recommended storage condition at 2°C – 8°C.

Stability at the long-term storage condition, at the accelerated storage conditions and at stressed storage conditions have been performed in line with relevant guidance.

Overall, the FP stability program follows ICH Q1A and ICH Q5C guidelines and the stability study protocols have been provided for all presentations and conditions.

All currently available long-term stability results met the stability acceptance criteria and are within the limits defined for commercial specification. No significant trends are observed in the tested quality attributes. Thus, the proposed shelf-life is supported by the currently available data. Once removed from the refrigerator, Osenvelt may be stored at room temperature (up to 25°C) for up to 30 days in the original container and should not be refrigerated afterwards. It must be used within this 30-day period. This can be agreed since from the stability studies at accelerated conditions all results met the acceptance criteria over the testing periods.

The photostability studies were performed according to ICH Q1B guideline. The results indicate that CT-P41 FP is photo-stable and adequately protected from exposure to light when stored in its secondary packaging.

No in-use stability studies were performed since no dilution or re-constitution is applicable for CT-P41 FP. This is agreed.

2.3.3.5. Biosimilarity

CT-P41 is a biosimilar product to the reference medicinal products (RMP) Prolia and Xgeva (denosumab) for subcutaneous (SC) use. Two biosimilars have been developed: Stoboclo (CT-P41 PFS 60 mg solution for injection (60 mg/mL)) to the reference product Prolia and Osenvelt (CT-P41 vial 120 mg solution for injection (70 mg/mL)) to the reference product Xgeva, respectively.

A common biosimilarity exercise supports both products submitted in separate MAAs.

A comprehensive similarity exercise following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012) has been performed.

CT-P41 60mg PFS and EU-Prolia are identical with respect to pharmaceutical form, concentration, and route of administration. CT-P41 120mg vial and EU-Xgeva are identical with respect to pharmaceutical form, concentration, and route of administration. The composition of CT-P41 is identical to that of EU-Prolia (PFS) but slightly different from that of EU-Xgeva (vial) in excipients.

Analytical similarity of CT-P41 is presented in a 3-way analytical similarity assessment using EU-authorised as well as US-licensed Prolia and Xgeva. In line with current legislation and guidelines, only data generated with the EU-Prolia/Xgeva batches is to be considered pivotal. Hence, the analytical similarity of CT-P41 is assessed compared to EU-Prolia and EU-Xgeva and the presented data of US-reference products is considered supportive information. The 3-way analytical similarity assessment also serves as a bringing study between EU-Prolia and US-Prolia and between EU-Xgeva and US-Xgeva. The clinical trials CT-P41 1.2 and CT-P41 3.1 supporting this MAA have been made with US-Prolia and clinical trial CT-P41 1.1 submitted as supportive information with EU-Prolia.

The establishment of QTPP has been presented. The QAs included in the similarity assessment are considered to cover relevant attributes of the products. The analytical similarity assessments included

a similarity analysis of primary and higher order structure, purity/impurity, content, glycan profiles and post-translational modifications, as well as biological assays.

CTP41 vial and PFS presentations have been demonstrated to be comparable in all quality attributes. The study design is considered adequate.

Batch selection of reference product batches included in the similarity assessment has been described. The reference product batches reflected a sufficient range of expiration dates and product ages. It can be concluded that the number and choice of batches is considered sufficient to demonstrate analytical similarity and the material used in the analytical biosimilarity studies is considered representative of the material (Prolia) used in clinical trials.

Scientific justification and discussion of the potential impact on clinical efficacy, PK, safety and immunogenicity is provided where differences were detected in physicochemical quality attributes.

Based on the presented data the applicant´s approach to demonstrate biosimilarity is considered appropriate.

Table 1 below includes a summary of the biosimilarity assessment including a critical evaluation of biosimilarity. The CT-P41 120 mg vial vs. Xgeva study was designed to confirm that the results of analytical similarity studies of CT-P41 60 mg PFS FP vs. Prolia remain relevant for CT-P41 120 mg vial FP vs. Xgeva. Hence, the numbers in the table represent the primary similarity study CT-P41 60 mg PFS FP vs. Prolia. The results from analytical similarity assessment of CT-P41 120mg vial compared to EU-Xgeva align with those presented for CT-P41 PFS and EU-Prolia.

Table 1. Summary of biosimilarity assessment

Molecular parameter	**Attribute**	**Methods**	**Key findings, conclusions**
Primary structure and PTMs	Intact mass (non-reduced/reduced)	reduced and non-reduced LC-MS	Similar intact mass (non-reduced). Similar deglycosylated intact mass (reduced).
	Primary sequence of HC and LC	Peptide mapping by LC-MS (sequence coverage)	Identical primary sequence with sequence coverage of 100%. The amino acid sequences were confirmed by MS/MS analysis.
	Deamidation	Peptide mapping by LC-MS (modification)	CT-P41 has lower level of deamidation. The difference in deamidation is small, and a lower level of deamidation modification would not adversely impact efficacy or safety.
	Oxidation		CT-P41 has lower level of oxidation. The differences in oxidation are small, and a lower level of oxidation would not adversely impact efficacy or safety.
	N-terminal variants		CT-P41 contained a very slightly higher level of HC and LC Glu01. This minor difference is not considered clinically significant.
	C-terminal lysine and proline amidation variants		CT-P41 has lower level of HC with C-terminal lysine than EU-Prolia. CT-P41 also has higher level of C-terminal variant without two terminal amino acids (lysine and glycine). CT-P41 has higher level of C-terminal proline amidation.

Molecular parameter	Attribute	Methods	Key findings, conclusions
			Differing levels of C-terminal lysine and proline amidation are not expected to impact biological function.
	N-terminal sequencing and C-terminal sequencing	Peptide mapping RP-UPLC+ MS/MS	The detected N-terminal and C-terminal sequences of the light and heavy chain matched the expected sequences of denosumab.
Charged variants	Isoelectric point, pI	cIEF	Similar peak pattern with comparable pI
	Charged variant groups	IEC-HPLC	CT-P41 samples contained a lower proportion of acidic peaks than EU-Prolia. Acidic peaks contain variants with glycation and deamidation and lower level in CT-P41 and is not considered to adversely affect efficacy or safety. CT-P41 samples contained a lower proportion of main peak than EU-Prolia CT-P41 contained a higher proportion of basic peaks than EU-Prolia. Basic peaks contain C-terminal proline amidation variants, which are unlikely to affect safety or efficacy. The observed differences in charge variant profiles are unlikely to have clinically meaningful impact.
Glycation and Glycosylation	Glycation	LC-MS after deglycosylation and reduction	Slightly lower level of glycation in CT-P41. Lower glycation level is highly unlikely to have an adverse impact on safety or efficacy.
	Oligosaccharide profiling	HILIC-UPLC-FLD	CT-P41 had a higher level of fucosylated group glycans. CT-P41 had slightly lower level of afucosylated group glycans. CT-P41 had notably lower level of high mannose group glycans. CT-P41 was highly similar to Prolia/Xgeva in galactosylated group glycans.
	N-linked glycan analysis	Peptide mapping with LC-MS	G0F was higher in CT-P41. Man5 was lower in CT-P41. The lower afucosylation level (more core fucoses) and lower high mannosylation level (also lacking core fucoses) are in line with the observed lower FcγRIIIa (V-type & F-type) binding affinity of CT-P41 compared to EU-Prolia. The differences in afucosylation and high mannosylation are not expected to adversely affect the overall conclusion of similarity because the primary MoA of denosumab is not mediated by Fc effector functions such as ADCC or CDC.
Purity / Impurity	Size variants (Monomer, HMW, LMW)	SEC-HPLC	Both products predominantly contain monomer, with low levels of HMW. LMW species were not detected. HMW level in CT-P41 was similar with EU-Prolia.
	Size variants (monomer content, molecular weight)	SEC-MALS	CT-P41 contains similar level of HMW with EU-Prolia.
	Size variants (aggregate content, monomeric purity)	AUC	%HMW of CT-P41 was similar or slightly lower with that of EU-Prolia. Observed difference is small and unlikely to adversely impact on clinical safety and efficacy.

Molecular parameter	Attribute	Methods	Key findings, conclusions
	Fragmentation (Intact IgG)	Non-reduced CE-SDS	Intact IgG level was similar.
	Fragmentation (LC+HC and non-glycosylated HC (NGHC))	Reduced CE-SDS	CT-P41 has higher level of %NGHC than EU-Prolia CT-P41 has a slightly lower level of purity (% H+L). An aglycosylation study demonstrated that NGHC level impacts FcγRIIIa-V binding affinity, but with levels higher than observed in CT-P41. FcγRIIIa binding can have an effect on ADCC activity, which is not MoA of denosumab. Higher % NGHC in CT-P41 is unlikely to have any adverse impact on immunogenicity, efficacy or safety.
Higher order structure	Secondary and tertiary structures	Circular dichroism (CD)	Similar secondary and tertiary structures as well as thermal stabilities.
	Thermal stability, thermal transition temperatures	Differential scanning calorimetry (DSC)	
	Secondary structure	Fourier transform infrared spectroscopy (FTIR)	
	Free thiols	DTNB method (Ellman's assay)	The level of free thiol groups in CT-P41 were slightly higher than in EU-Prolia. Overall, the free thiol level was so low that the minor difference has no effect on antibody structure.
	Disulphide bonds	Non-reduced peptide mapping	Similar disulphide bonds.
	IgG2 Isoforms	RP-UPLC	CT-P41 is similar to EU-Prolia in the ratio of IgG2 disulphide bond isoforms. The B isoform was the predominant form in both products.
Content	Protein concentration	UV_{280nm} by SoloVPE	Similar protein concentrations. Target protein concentration for CT-P41 PFS is 60 mg/ml. Target protein concentration for CT-P41 vial is 70 mg/ml (120 mg/1.7 mL)
Fab binding related biological activity	RANKL binding	ELISA	Fab binding related assays demonstrate high similarity.
	Cell-based RANKL binding	Cell-based binding assay (CELISA)	
	RANKL binding inhibition Assay with RANK	ELISA	
	RANKL binding inhibition Assay with OPG	ELISA	
	Osteoclastogenesis Inhibition Assay	in vitro cell-based assay	
	C1q binding	ELISA	Similar C1q binding.

Molecular parameter	Attribute	Methods	Key findings, conclusions
Fc binding related biological activity	FcγRIIIa (V/F-type)	SPR	CT-P41 has lower binding to FcγRIIIa (V/F-type). The difference is addressed to the slightly lower level of afucosylated glycans (including lower level of high mannose glycans). FcγRIIIa may affect ADCC binding, however similar lack of ADCC was observed. As ADCC activity is not relevant for the MoA of denosumab, the difference is not considered clinically relevant.
	FcγRIIa, FcγRIIb,	SPR	Similar binding.
	FcγRIa, FcγRIIIb	SPR	Similar lack of binding. (additional MoA studies only with CT-P41 PFS and Prolia)
	FcRn binding	SPR	Similar FcRn binding.
	ADCC and CDC activity	ADCC: effector cell assay (tmRANKL-overexpressing CHO-K1 cells as target cells and human PBMCs as effector cells. CDC: tmRANKL-overexpressing CHO-K1 cells as target cells	Similar lack of ADCC and CDC activities. (additional MoA studies only with CT-P41 PFS and Prolia)
Forced degradation	High temperature (55 ± 5 °C) Chemical oxidation Photostability (UV light) Low/high pH	peptide mapping (LC/MS), IEC-HPLC oligosaccharide profiling SEC-HPLC reduced/non-reduced CE-SDS RANKL binding inhibition FcRn binding	Despite a few differences in the values for individual attributes, the overall degradation profiles of both PFS and vial presentations of CT-P41 and EU-Prolia/Xgeva products are similar under high temperature, chemical oxidation, UV light, low pH and high pH stress conditions. The differences in the degradation profiles are considered minor and not clinically meaningful. The presented degradation profiles support the claim for biosimilarity.
Thermal stability	Accelerated stability (25±2°C/60±5% RH) Stressed stability (40±2°C/75±5% RH)	Same methods as for forced degradation studies	Thermal stability data demonstrate broadly similar stability trends, such as increasing acidic and basic peaks and decreasing main peak by IEC-HPLC, and sightly decreasing purity by reduced/non-reduced CE-SDS and SEC-HPLC. Thermal stability studies support the biosimilarity claim.

Similarity between CT-P41 and EU-Xgeva has been demonstrated for the following physicochemical and biological properties:

- Primary structure and post-translational modifications
- Charged variants
- Glycation and glycosylation
- Purity/impurity (size variants)
- Higher order structure

- Content (protein concentration)
- Comparative stability studies (forced degradation, accelerated and stressed stability)
- Biological activity
  - Fab binding related (RANKL binding, Cell-based RANKL binding, RANKL binding inhibition Assay with RANK, RANKL binding inhibition Assay with OPG, Osteoclastogenesis Inhibition Assay
  - Fc binding related (C1q, FcγRIIIb, FcγRIIa, FcγRIIb, and FcγRIa, FcRn as well as lack of ADCC and CDC activity)

The totality of the presented biological and physiochemical data supports the claim of biosimilarity for CT-P41 and EU-Prolia/Xgeva.

All biological activities relevant to the primary mechanism of action, including osteoclastogenesis inhibition assay, RANKL binding inhibition assay (with OPG / RANK), RANKL binding assay and cell-based RANKL binding assay, are similar. A lower binding activity of CT-P41 to FcγRIIIa (158V and 158F) compared to EU-Prolia/Xgeva was observed and attributed to lower levels for afucosylated glycans and lower level of high mannose glycans in CT-P41. These differences are not considered to be clinically meaningful based on the similar lack of ADCC activity for both CT-P41 and EU-Prolia. Also, differences in PK studies between the proposed biosimilar and the US-reference product were not seen and the mannosylation levels in US- and EU-reference products are similar. The observed difference in mannosylation is not expected to have an effect on clinical performance.

Differences were also observed in heavy chain deamidation and oxidation, C-terminal lysine and proline amidation and consequently in cIEF peak pattern and IEC-HPLC peak ratios. Furthermore, minor differences were observed in glycation levels and NGHC levels in CT-P41 compared to reference medicinal product. These differences are considered not to be clinically relevant. All observed differences are well discussed and justified, are not considered to be clinically meaningful, and are unlikely to have an impact on PK, efficacy, or safety.

In conclusion, biosimilarity versus the EU reference medicinal product was sufficiently demonstrated. In addition, the data provided demonstrate that US-Prolia used in the comparative clinical trial is representative of the EU reference medicinal product.

2.3.3.6. Adventitious agents

No human origin raw materials were used in the manufacturing process of CT-P41. However, some animal derived raw materials were used. Appropriate TSE risk assessment was provided for all animal derived raw materials.

Cell banks (MCB, WCB and EPCB) were extensively characterised for both endogenous viruses and adventitious viral contamination. The unprocessed bulk harvests originating from several commercial scale batches were tested for viruses.

The model viruses were chosen in accordance with ICH Q5A (R1) to represent a combination of RNA and DNA viruses, enveloped and non-enveloped viruses, and a wide range of virus families of variable particle size and chemical resistance

Scale-down models of the commercial purification process were used in the viral clearance studies. The comparison of process parameters between scale-down model and commercial scale production was demonstrated. Description and qualification data of methods used in the viral clearance studies including the suitability of these procedures to quantify the (model) virus particles are provided. The

overall cumulative reduction is considered safe and acceptable. Therefore, an adequate safety margin exists in the CT-P41 manufacturing process for retrovirus inactivation/removal.

Overall, the viral clearance studies were performed in accordance with ICH Q5A guideline and demonstrate adequate capacity of the production process to inactivate or remove viruses.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Osenvelt has been developed as a similar biological medicinal product (biosimilar) to the reference medicinal product Xgeva. Its active substance denosumab is manufactured using a typical manufacturing process for monoclonal antibodies.

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner.

The FP is manufactured according to a standard process. The manufacturing process is appropriately described, and process parameters are sufficiently justified based on process characterisation and validation data. The validation of the manufacturing process has been satisfactorily demonstrated ensuring the manufacturing process for Osenvelt is capable of consistent and robust performance.

Biosimilarity versus the reference product was sufficiently demonstrated. In addition, the data provided demonstrate that US-Prolia used in the comparative clinical trial is representative of the EU reference medicinal product. From the quality perspective, Osenvelt is approvable as proposed biosimilar to Xgeva. No quality aspects impacting on the Benefit-Risk balance have been identified.

Overall, 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.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Osenvelt is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the marketing authorisation application for Osenvelt is considered approvable from the quality point of view.

2.3.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended a point for further investigation.

2.4. Non-clinical aspects

2.4.1. Introduction

A battery of *in vitro* pharmacodynamic (PD) studies have been performed to demonstrate the similarity between denosumab CT-P41 120 mg (70 mg/mL) and EU-/US-Xgeva. *In vitro* similarity assays on PD activities such as osteoclastogenesis inhibition, RANKL binding inhibition (ELISA), RANKL binding affinity (ELISA), cell-based RANKL neutralisation assay, and FcγRⅢa (F-type and V-type), FcγRⅡa and

FcγRⅡb, FcRn binding affinity (SPR), and C1q binding assay (ELISA) have been performed to demonstrate similarity in the mode of action among CT-P41 and EU-/US-Prolia as a part of quality evaluation. Additionally, antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), FcγRI and FcγRIIIb binding affinity (SPR) was evaluated to confirm lack of activity and affinity for CT-P41 DP and Prolia.

An *in vivo* 4-week repeat-dose toxicology study with toxicokinetic (TK) assessment has been performed in cynomolgus monkeys . The electroluminescence ligand binding assay was used for detection of drug substances and anti-drug antibodies (ADA) in cynomolgus monkey serum.

Relevant EMA guidelines were followed in the development of biosimilar medical product with exception that no *in vivo* data is required in the EMA/CHMP/BMWP/403543/2010 if the *in vitro* non-clinical studies confirm the biosimilarity. The toxicity study in cynomolgus monkeys was performed to comply with requirements of non-EU (global) authorities and is considered as supportive information in this EU application.

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 CT-P41 (70 mg/ml) and EU-/US-Xgeva to demonstrate the biosimilarity. All *in vitro* studies data were included under the Quality dossier, and to avoid repetition of data, the results are only shortly summarised under the non-clinical assessment. Please see Quality/Biosimilarity assessment for further details.

The formulation of CT-P41 is slightly different from the EU-Xgeva in excipients. As excipients are considered to be clinically inactive components, the identified difference is not considered to have an impact on the biological activities of the CT-P41 (70 mg/ml).

The key biological assays (Fab binding and complement/Fc binding) showed highly similar biological activities for CT-P41, and EU-Xgeva. Please see Quality/Biosimilarity assessment for further details.

No *in vivo* PD studies have been conducted. This is acknowledged.

2.4.2.2. Secondary pharmacodynamic studies

Secondary PD studies are not required for similar biological medicinal products.

2.4.2.3. Safety pharmacology programme

Safety pharmacology studies are not required for similar biological medicinal products, however, these endpoints were incorporated in the 4-week repeat dose toxicity study in cynomolgus monkeys. No differences were noted in regards the safety pharmacology endpoints in the 28-day repeat-dose toxicity study in cynomolgus monkeys.

2.4.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies are not required for similar biological medicinal products.

2.4.3. Pharmacokinetics

Validated immunoassay was used to quantify the CT-P41 60mg/mL and US-Prolia as well as associated anti-drug antibody concentrations in the cynomolgus monkey serum. Validated UV-SPEC method was used to analyse the total protein concentration and SEC-HPLC-UV method was used to analyse the formulation stability of CT-P41/US-Prolia in formulation buffer . Acceptance criteria of applicable important attributes were met (e.g. specificity, accuracy, sensitivity, precision, and stability).

For ADA determination, one control female was found to be ADA positive on day 29 (number 1501), indicating that the assay may also detect reactive antibodies which are not specific to the test-materials. Furthermore, low levels of anti-drug antibodies might not have been reported. No further ADAs were detected in animals of any other treatment group.

No stand-alone PK studies have been performed as part of the CT-P41 development (comparative) program. TK analysis of 4-week repeat-dose monkey study with CT-P41 and US-Prolia is evaluated in the Toxicology section.

No distribution, metabolism or excretion studies, comparative studies assessing PK drug interactions or other PK studies are required for biosimilars.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

Single dose toxicity studies are not required for biosimilars.

2.4.4.2. Repeat dose toxicity

A GLP compliant 28-day repeat-dose toxicity study , including TK and immunogenicity evaluation, was conducted in cynomolgus monkeys. The toxicity and TK profiles of CT-P41 60mg/mL and US-Prolia were compared to comply with the requirements of authorities not within the EU. Monkeys (3 males and 3 females/group) received vehicle or 10 mg/kg dose once weekly via subcutaneous (SC) administration for 4 weeks (a total of 4 doses).

The CT-P41 batch used in the 4-week monkey study was manufactured using the nonclinical manufacturing process (Process A; lot number 20P16B01), i.e., a pilot scale process. As quality analyses have demonstrated that each process was comparable in their biological activities, the CT-P41 batch used in the study is foreseen representative with the clinical batches.

The applicant is reminded about the 3R principles and that the EU guideline for biosimilar medicinal products does not include recommendation on conducting *in vivo* studies. However, it is understood that the monkey study was performed for global development purposes. This study is considered representative also for CT-P41 70 mg/mL and EU/US-Xgeva comparison, and the data are considered as supportive for the EU marketing authorisation application for CT-P41.

The overall picture of the toxicity is similar for the CT-P41 and US-Prolia. The dose of 10 mg/kg/week was well tolerated for both products (NOAEL). Alterations in calcium, phosphorus and ALP activity, correlating with microscopic changes at low severity as increased trabecular bone in males and females, but without corresponding clinical signs or indication of bone fragility, were observed and not considered adverse. Furthermore, a test-article related increased incidence of watery faeces was noticed in male and female CT-P41 treated animals and females treated with Prolia, which was

apparently more pronounced in CT-P41 treatment groups. The differences seen between the animals treated with the medicinal products under comparison are minor, and as limitations of animal models (e.g., sensitivity and variability) are well-known, these differences are not considered to have an effect on the biosimilarity assessment of CT-P41 and (EU)/US-Prolia.

2.4.4.3. Genotoxicity

Genotoxicity studies are not required for biosimilars.

2.4.4.4. Carcinogenicity

Carcinogenicity studies are not required for biosimilars.

2.4.4.5. Reproductive and developmental toxicity

DART studies are not required for biosimilars.

2.4.4.6. Toxicokinetic data

The TK analysis did not suggest any difference between males and females. The C_{max} and AUC values were comparable between CT-P41 and US-Prolia. Some variation between individuals was observed, and as number of animals is low (n=3), the differences in the mean C_{max} and AUC values are mainly explained by intraindividual variation (SD). The data is presented in the table below. No markable differences in mean or individual accumulation ratios were recorded. The applicant's conclusions regarding comparability of TK data for CT-P41 and US-Prolia are accepted as no differences were reported in *in vitro* functional parameters thus demonstrating biosimilarity.

Table 2. Mean CT-P41 and US-Prolia TK parameters in monkey serum

Study ID/ species	Dose mg/kg/week	Study day	Animal $AUC_{0\text{-}168hr}$ (ng·h/ml) (SD)		C_{max} (ng/ml) (SD)	
			♂	♀	♂	♀
cynomolgus monkeys	10 CT-P41	1	15600000 (650000)	12600000 (1400000)	130000 (8390)	93200 (6260)
	10 US-Prolia	1	14200000 (1060000)	13400000 (1390000)	108000 (13900)	111000 (22200)
	10 CT-P41	22	50200000 (5730000)	32200000 (7330000)	328000 (36000)	239000 (50600)
	10 US-Prolia	22	38800000 (2690000)	23500000 (7990000)	282000 (40100)	193000 (18800)

2.4.4.7. Local tolerance

No differences were reported concerning the local tolerance in the site of SC injection in monkeys treated with CT-P41 and US-Prolia.

2.4.4.8. Other toxicity studies

Antigenicity

No anti-CT-P41 or anti-US-Prolia antibodies were detected in the 4-week repeat-dose toxicity study, and therefore no differences in the comparison of CT-P41 and US-Prolia were identified in their ADA response. It should be noted that these data have only low predictivity for the immunogenicity potential in humans.

2.4.5. Ecotoxicity/environmental risk assessment

The use of medicinal product Osenvelt is not expected to pose a risk to the environment as the active substance denosumab is a natural product (protein), therefore its use will not alter the concentration of distribution of the substance in the environment.

2.4.6. Discussion on non-clinical aspects

The comparability assessment strategy for denosumab CT-P41 and EU-Xgeva focused on the battery of receptor-binding studies or cell-based *in vitro* assays. In addition, an *in vivo* toxicity study was performed to compare CT-P41 60 mg/mL to its reference product US-Prolia. As no *in vivo* toxicity data is required for the comparability assessment in the EU, this data is considered to be only supportive.

Pharmacodynamics

The demonstration of biosimilarity of CT-P41 and EU-Xgeva was focusing on the battery of receptor-binding studies or cell-based *in vitro* assays. These studies are discussed in the quality/biosimilarity assessment.

The formulation of CT-P41 is slightly different from the EU-Xgeva in excipients. As excipients are considered to be clinically inactive components, the identified difference is not considered to have an impact on the biological activities of the CT-P41 (70 mg/ml).

No secondary pharmacology or pharmacodynamic interactions studies were conducted with CT-P41 and EU-Xgeva. These studies are not required for a biosimilar. No differences in the safety pharmacology endpoints were observed in the CT-P41 60 mg/mL and its reference product US-Prolia treated monkeys in the supportive 4-week repeat-dose toxicology study.

Pharmacokinetics

No stand-alone PK studies have been performed as part of the CT-P41 development (comparative) program. TK analyses of supportive 4-week repeat-dose cynomolgus monkey study with CT-P41 and US-Prolia showed comparable C_{max} and AUC values between CT-P41 and US-Prolia. As no differences were reported in *in vitro* functional parameters, possible differences in the PK of CT-P41 and EU-Prolia are unlikely.

Toxicology

The supportive 4-week repeat-dose study in cynomolgus monkeys showed only minor differences in the toxicity between the animals treated with the medicinal products CT-P41 and US-Prolia. These differences are not considered to have an effect on the biosimilarity assessment of CT-P41 and EU/US-Prolia.

ERA

Denosumab is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Osenvelt is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

The available non-clinical data supports the biosimilarity when compared 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**

Table 3. Clinical studies of CT-P41

CT-P41 1.1 (Pilot study)	**Primary Objective:** To evaluate safety in terms of treatment-emergent AEs of CT-P41, compared to that of EU-Prolia **Secondary Objective:** To evaluate the additional safety, immunogenicity, PK and PD of CT-P41 and EU-Prolia Healthy male subjects Randomised: 32 CT-P41 60 mg: 16 EU-Prolia 60 mg: 16	Phase 1, randomised, double-blind, two-arm, parallel group, single-dose study to evaluate the safety and PK of two formulations (CT-P41 and EU-Prolia) of denosumab	**Test product:** CT-P41, 60 mg/1 mL by SC injection to the upper arm via PFS as a single administration **Reference product:** EU-Prolia, 60 mg/1 mL by SC injection to the upper arm via PFS as a single administration	**Secondary endpoints**: **PK:** -$AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, T_{max}, $T_{1/2}$, %AUCext, λz, CL/F, and Vz/F **PD:** -%change from baseline of s-CTX -%change from baseline of P1NP **Immunogenicity:** -Incidence and titre of ADA -Incidence of NAb
CT-P41 1.2 (Pivotal PK study)	**Primary Objective:** To demonstrate the PK similarity between CT-P41 and US-Prolia in healthy male subjects **Secondary Objective:** To evaluate the additional PK, PD, safety, and immunogenicity of CT-P41 and US-Prolia Healthy male subjects Randomised:154 CT-P41 60 mg: 76 US-Prolia 60 mg: 78	Phase 1, randomised, double-blind, two-arm, parallel group, single-dose study to compare PK, PD and safety of two formulations (CT-P41 and US-Prolia) of denosumab	**Test product:** CT-P41, 60 mg/1 mL by SC injection to the upper arm via PFS as a single administration **Reference product:** US-Prolia, 60 mg/1 mL by SC injection to the upper arm via PFS as a single administration	**Primary PK endpoints:** -$AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max} **Secondary endpoints:** **PK:** **-**$pAUC_{0\text{-}W16}$**,** $pAUC_{W16\text{-}inf}$, T_{max}, $T_{1/2}$, %AUCext,λz, CL/F, Vz/F, MRT **PD:** -AUEC of s-CTX and P1NP over the study period and %change from baseline of s-CTX and P1NP at each visit **Immunogenicity:** -Incidence of ADA and NAb -ADA titre
CT-P41 3.1	**Primary Objectives:**	Phase 3, double-blind, randomised,	**Treatment Period I (52 weeks):**	**Co-primary endpoint:** **PD:**

(Comparative efficacy and safety study)	To demonstrate the equivalence of CT-P41 to US-Prolia in terms of efficacy in postmenopausal women with osteoporosis To demonstrate the PD similarity in terms of area under the effect curve (AUEC) of serum carboxyterminal cross-linking telopeptide of type I collagen (s-CTX) **Secondary Objective:** To evaluate the efficacy, PK, PD, and safety including immunogenicity of CT-P41 and US-Prolia Postmenopausal women with osteoporosis <u>First Randomised:</u> 479 CT-P41 60 mg: 240 US-Prolia 60 mg: 239 <u>Second Randomised in</u> Treatment Period II Subset: 422 * CT-P41 Maintenance: 221 US-Prolia Maintenance: 100 Switched to CT-P41: 101	active-controlled, phase 3 study to compare efficacy, PK, PD, and safety of CT-P41 and US-Prolia	Two doses of CT-P41 or US-Prolia by SC injections using a PFS every 6 months (Q6M) (at Weeks 0 and 26) - Arm 1: CT-P41 60 mg -Arm 2: US-Prolia 60 mg **Treatment Period II (26 weeks):** One dose of CT-P41 or US-Prolia by SC injection using a PFS study drug 60 mg (at Week 52) -Arm 1: CT-P41 60 mg -Arm 2-1: US-Prolia 60 mg -Arm 2-2: CT-P41 60 mg All patients were to also receive daily supplementation containing at least 1,000 mg of elemental calcium and at least 400 IU vitamin D.	-Area under the effect curve of s-CTX over the initial 6 months (from Day 1 predose to Week 26 predose) **Secondary endpoints:** **PK:** -Denosumab concentrations and C_{trough} up to week 78 -C_{max}, AUC_{0-t}, T_{max}, V_d and $t_{1/2}$ after the first dose **PD:** -AUEC of serum s-CTX and P1NP over the study period, -%change from baseline of s-CTX and P1NP at weeks 26, 52 and 78. **Immunogenicity:** -Incidence of ADA and NAb

2.5.2. Clinical pharmacology

Denosumab CT-P41 (a recombinant monoclonal antibody [mAb]) was developed as a biosimilar to the innovator denosumab products i.e., Prolia and Xgeva, marketed by Amgen. Prolia and Xgeva contain same active ingredient at two different strengths with two different presentations:

- Prolia 60 mg/ml PFS
- Xgeva 120 mg/1.7 ml single use vial

The CT-P41 presentation 'Osenvelt 120 mg/1.7 ml vial' corresponds to the Xgeva 120 mg/1.7 mg vial.

The clinical development program included 3 clinical studies to demonstrate PK and PD similarity between CT-P41 and Amgen's denosumab as summarised in the table above.

2.5.2.1. Pharmacokinetics

Bioanalytical methods

All bioanalytical methods used in the MAA were fully validated by PPD Laboratory Services for Celltrion, Inc.. A detailed assessment for each analytical method is provided below.

<u>Quantification of denosumab concentration in human serum</u>

Biosimilar candidate CT-P41 and the originator US-Prolia seemed to perform according to analytical similarity in terms of selectivity, precision and accuracy. In addition, the dilution linearity and hook effect were carried out and considered acceptable. Both parallelism and long-term stability of

denosumab (up to 468 days at -80°C) were evaluated in separate appendixes acceptably. It should be noted that analytical method validation plan (RPLX2) was lacking all other certificates of critical reagents than CT-P41 itself, but most were later shown in amendments (RPLX3 and RPLX6).

The analyses of clinical samples both in healthy male subjects (CT-P41 1.1 and 1.2) as well as in postmenopausal women with osteoporosis (CT-P41 3.1) were reliable within the given accuracy and precision ranges. The reasons for repeat analysis were acceptable and the required criteria for incurred sample reanalysis were met.

Determination of C-telopeptide of collagen type 1 (serum CTX-1) and total procollagen type 1 N-terminal propeptide (P1NP) in human serum

Putative osteoporosis biomarkers CTX-1 and P1NP were determined from human serum using commercially available platform measuring multiple analytes simultaneously. The validation studies were conducted both in Europe and US and with many instruments, but thorough and appropriate cross validation study has been executed and report included in the submission. The validation data is based on Total Allowable Error (TaE) concept, whereas specificity, selectivity and stability of for the determination of CTX-1 and total P1NP in human serum was taken from manufacturer's packet insert.

In these multi-analytical systems, no detailed information is provided upon critical reagents, such as CTX-1 (termed here as β-CrossLaps) or P1NP, but since detailed cross validation is performed with thorough lot-to-lot variation testing on used reagents and calibrators, the provided data is considered adequate and acceptable.

In addition, for preparation of the quality controls, ICH M10 guideline suggests that the analyte should be spiked at the LLOQ, within three times of the LLOQ (low QC), around the geometric mean of the calibration curve range (medium QC), and at least at 75% of the ULOQ (high QC) and at the ULOQ. Calibration range for CTX-1 was 50-2000 pg/mL. However, respective QCs (PreciControl Varia) used for monitoring the assay's accuracy and precision had concentrations of approximately 320 pg/mL (QC1) and 750 pg/mL (QC2). For the validated reference range of CTX-1 in females the applicant refers to the provided manufacturer's kit insert, where premenopausal women (n = 254) had a mean (±SD) value of 299 (±137) pg/mL β-CTX (mean + 2 SD: 573 pg/mL). Postmenopausal women (n = 429) had a mean (±SD) value of 556 (226) pg/mL (mean + 2 SD: 1008 pg/mL) β-CTX.

Calibration range for P1NP was 25 ng/mL-850 ng/mL. Respective QCs (PreciControl Varia) used for monitoring the assay's accuracy and precision had concentrations of approximately 30 ng/mL and 200 ng/mL. For the validated reference range of CTX-1 in females, the applicant refers to the provided manufacturer's kit insert, where premenopausal women (n = 129) had mean levels (5% percentile, median, 95% percentile) of total P1NP of 30.10 ng/mL (15.13, 27.80, 58.59), in postmenopausal women without hormone replacement therapy (HRT; (n = 290) had a mean value of 45.05 ng/mL (20.25, 42.94, 76.31) and in postmenopausal women with HRT (n = 154) the mean value was 31.74 ng/mL (14.28, 28.48, 58.92).

The applicant, furthermore, states that the reference range taken from manufacturer's kit insert and was verified by the applicant by analysing samples collected from healthy volunteers (CTX-1: 4447 samples, total P1NP: 4450 samples). The reference range was established by the Medical Director after reviewing assay information and relevant scientific and medical literature.

Also, correlation was used to demonstrate the closeness and comparability of the results obtained between instruments. The two methods were considered equivalent, if the slope was ≤5% within lab and the intercept was within 1SD of observed precision. The correlation coefficient should be ≥0.975. The applicant states that TP1NP showed a slope of 0.860 on the E602-1 module and therefore exceeded the 5% limit of acceptability for the instrument. The applicant states that acceptability of results throughout the entire validation period was based on the concept of Total Allowable Error (TaE).

Total Error (TE) was calculated as %bias + (1.65 x %CV), and each method was considered acceptable if results met "%TE ≤ %TaE" criteria. For total P1NP %TE was 17.69, which was below the %TaE of 20.5%.

From clinical studies CT-P41 1.2 and CT-P41 3.1, the analytical report of biomarkers CTX-1 and P1NP has been provided. All calibrations and quality control data show acceptable performance.

Determination of anti-drug antibodies in human serum

The three-tiered approach was utilised in determination of ADAs and the assay was validated for its precision, selectivity, sensitivity, drug tolerance, target interference, prozone effect and stability. The intra- and inter-assay precisions both for screening, confirmation and selectivity met the acceptance criteria except for the NC in intra-assay precision data: %CV of 123% for the % inhibition (after outlier exclusion) vs %CV ≤ 20.0% as specified in the validation plan. However, all contributing single NC % inhibition results were below the confirmatory cut point after removal of the outlier and the %CV for the NC inhibited RLU was 6.87% (≤ 20.0%). Hence, the intra-assay precision data can be considered acceptable. All acceptance criteria specified in the method validation plan for inter-assay precision were met. Inter-assay precision (%CV) of PC were <20.0% for uninhibited RLU, inhibited RLU and % inhibition. Inter-assay precision of NC was <20.0% for uninhibited RLU and inhibited RLU but 54.9% for % inhibition.

The sensitivity based on the healthy cut points was 2.88 ng/mL in the screening assay and 3.84 ng/mL in the confirmatory assay. The sensitivity based on disease-state (osteoporosis) cut points was 2.58 ng/mL in the screening assay and 4.69 ng/mL in the confirmatory assay.

Cut points for the screening and confirmation assay in healthy subjects were determined in 50 individual drug-naïve healthy human serum samples with no detectable ADA activity. Cut points for the screening and confirmation assay in diseased state (osteoporosis) subjects were determined in 45 individual drug-naïve osteoporosis human serum samples with no detectable ADA activity. For confirmatory cut-points, human sera were spiked with an excess of drug prior to analysis. Defined cut points (cut point value [CPV]; % signal inhibition) were 1.10 (Screening Assay Cut Point – Healthy), 28.5% (Confirmatory Assay Cut Point – Healthy), 1.22 (Titration Assay Cut Point – Healthy), 1.08 (Screening Assay Cut Point – Disease State), 31.4% (Confirmatory Assay Cut Point – Disease State), 1.20 (Titration Assay Cut Point – Disease State).

Selectivity was assessed with 10 human serum samples from healthy donors and 10 samples from diseased state (osteoporosis) donors spiked and non-spiked with anti-denosumab antibodies. Overall, the matrix interference data (selectivity) met the acceptance criteria.

Drug equivalence between CT-P41 drug product, US Prolia, and EU Prolia was demonstrated. No apparent hook effect was observed at concentrations up to 25,000 ng/mL of positive control. The drug tolerance at 25.0 ng/mL antibody concentrations was observed up to 50.0 µg/mL of CT-P41, EU Prolia, and US Prolia. The assay was tolerant to haemolytic and lipemic samples and to RANKL (target) up to 75.0 pg/ml. Benchtop (24 hours at RT) and freeze/thaw (6 F/T cycles) stability of serum samples was confirmed.

Critical reagents, drugs, and antibodies were well described. As a positive control, human anti-denosumab antibody was used. Taken together, the three-tiered approach for determination of ADAs was well described and developed. It can be considered state of the art and is valid for its intended use as long as the requested information is provided.

The applicant provided the ADA analytical reports from clinical studies CT-P41 1.1, 1.2 and 3.1. The analysis of clinical samples deemed to be reliable within the given accuracy and precision ranges. From

healthy individuals ADA positive samples were 60% and from disease patients 56% after confirmatory tier, whereafter they we subjected to further titration analysis.

Determination of neutralizing antibodies from human serum

An assay with was developed and validated by PPD Laboratories in order to detect neutralizing activity of ADAs against denosumab (NAb).

The assay was validated for its precision, selectivity, sensitivity, drug tolerance, target interference, prozone effect and stability. Intra- and inter-assay precision data met the acceptance criteria (%CV≤20%). The sensitivity based on healthy cut points was 56.7 ng/mL and 79.5 ng/mL based on disease state (osteoporosis) cut points.

The cut point for the screening assay in healthy subjects was determined in 50 individual drug-naïve human serum samples with no detectable NAb activity. The screening and titration assay cut point values were 0.904 and 0.893, respectively. The cut point for the screening assay in diseased state (osteoporosis) subjects was determined in 45 individual drug-naïve osteoporosis human serum samples with no detectable NAb activity. The screening and titration assay cut point values were 0.865 and 0.830, respectively.

Selectivity was assessed with 10 human serum samples from healthy donors and 10 samples from diseased state (osteoporosis) donors spiked and non-spiked with anti-CT-P41 NAb. Overall, the matrix interference data (selectivity) met the acceptance criteria.

No apparent hook effect was observed at concentrations up to 25,000 ng/mL of anti-drug neutralizing antibody sample.

To evaluate drug tolerance, anti-CT-P41 NAb were separately spiked with CT-P41. Drug tolerance at 250 ng/mL of neutralizing antibody was observed up to 15.0 µg/mL of CT-P41, US Prolia, or EU Prolia. Detection of anti-CT-P41 NAbs was tolerant to haemolytic and lipemic samples and to RANKL (target) up to 100 pg/ml. Benchtop (24 hours at RT) and freeze/thaw (6 F/T cycles) stability of serum samples was confirmed.

Critical reagents, drugs and antibodies were well described.

Taken together, the method for the detection of anti-CT-P41 (anti-denosumab) neutralizing antibodies in human serum was well described and developed.

The applicant provided full NAb analytical reports of serum samples from three clinical studies CT-P41 1.1., 1.2 and 3.1. The selected controls were appropriate and showed acceptable precision and linearity. Interference was not observed. Thus, no concerns are pursued regarding the methodology, but surprisingly low number of neutralizing antibodies (less than 1%) may reflect the poor sensitivity of the method. However, this low proportion compares well to the results of the originator and thus can be considered acceptable.

Study CT-P41 1.1 (Pilot study)

This study was a pilot phase 1, randomised, double-blind, two-arm, parallel group, single-dose study, which was designed to evaluate the safety, immunogenicity, PK/PD of CT-P41 and EU-approved Prolia in healthy male subjects.

Overall, 32 subjects were randomised in a 1:1 ratio to receive a single dose (60 mg) of CT-P41 or EU-approved Prolia. Subjects were stratified by body weight (< 80 kg *versus* ≥ 80 kg) measured on Day -1 as a part of the randomisation for balanced distribution. A total of 30 subjects were administered study drug (15 subjects in each treatment group), and 27 subjects completed the study (12 subjects in the CT-P41 treatment group and 15 subjects in the EU-approved Prolia treatment group). Only 3

subjects in the CT-P41 treatment group discontinued from the study after study drug administration due to lost to follow up (n =1 subject) and informed consent withdrawal (n = 2 subjects).

A study drug (CT-P41 [batch 0P1A02, protein content 57.2 mg/ml, expiry date March 2021] or EU-approved Prolia [batch 1117194, protein content 59.6 mg/ml, expiry date Oct 2022]) was administered subcutaneously (SC) via PFS on Day 1 (after an overnight fasting for at least 8 hours) and subjects were followed up for 134 days for safety, immunogenicity, PK and PD assessments.

The details of the study design and methods are presented in Section 2.5.8 "Clinical Safety".

For PK assessments blood was collected at pre-dose, and 6, 12, 24, 48, 72, 120, 168, 240, 336, 504, 672, 1008, 1344, 1680, 2016, 2520, and 3192 hours (day 134) after start of administration.

The PK secondary endpoints were: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, T_{max}, $T_{1/2}$, $\%AUC_{ext}$, λ_z, CL/F, and Vz/F

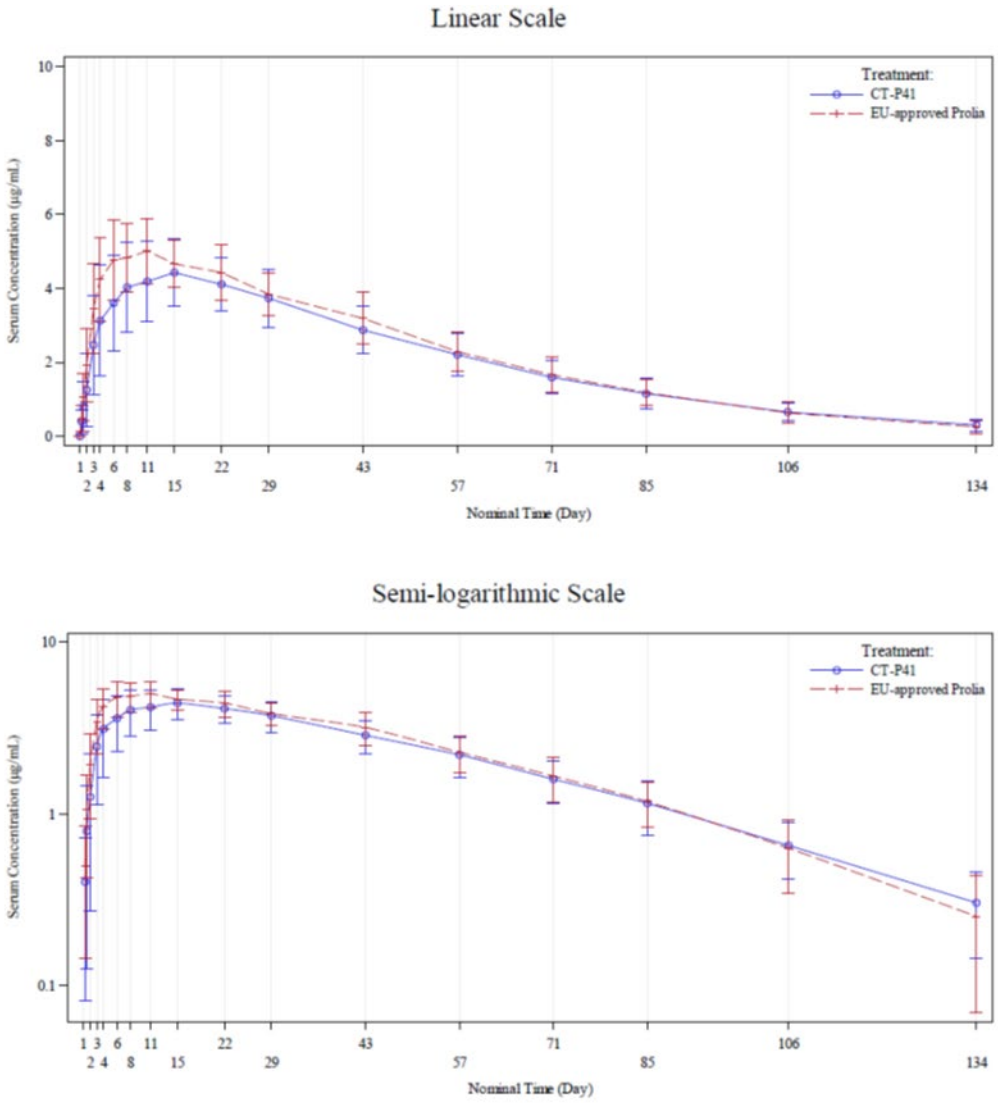
PK data analysis

Pharmacokinetic (PK) parameters were calculated using Phoenix WinNonlin Version 8.0 (Certara, Inc., Princeton, New Jersey, USA).

PK analyses were performed on the PK population. The PK endpoints were calculated using non-compartmental methods.

PK results

Mean (±SD) serum concentrations of denosumab observed until Day 134 (3192 hours post-dose) following a single administration of CT-P41 (60 mg) or EU-approved Prolia (60 mg) were generally comparable between the 2 treatment groups in the PK population as shown in Figure 1.



Abbreviations: EU, European Union; PK, pharmacokinetic(s); SD, standard deviation.
Source: Post-text Figure 14.2.2.1.1.

Figure 1. Mean (±SD) serum concentrations of denosumab by treatment (linear and semi-logarithmic scales) (PK population)

Serum PK parameters were comparable across both treatments (see Table 4).

Table 4. Serum PK parameters of denosumab by treatment group (PK population)

Parameter (unit) Statistics	CT-P41 (N=15)	EU-approved Prolia (N=15)
$AUC_{0\text{-last}}$ (day•µg/mL)		
n	15	15
Mean (SD)	227.371 (99.0871)	284.503 (54.8854)
CV%	43.5795	19.2917
Geometric mean	175.980	279.299
Median	246.624	287.596
Minimum, maximum	7.52, 327.10	183.60, 370.85
$AUC_{0\text{-inf}}$ (day•µg/mL)		
n	13	15
Mean (SD)	271.111 (61.9678)	293.450 (60.5848)
CV%	22.8570	20.6457
Geometric mean	262.464	287.315
Median	277.481	288.867
Minimum, maximum	114.51, 343.63	185.56, 380.95
$\%AUC_{ext}$ (%)		
n	13	15
Mean (SD)	4.533 (3.9053)	2.757 (2.5880)
CV%	86.1496	93.8771
Geometric mean	3.141	1.822
Median	3.263	2.651
Minimum, maximum	0.30, 14.81	0.31, 10.47
C_{max} (µg/mL)		
n	15	15
Mean (SD)	4.723 (0.9508)	5.277 (0.8563)
CV%	20.1321	16.2263
Geometric mean	4.626	5.208
Median	4.760	5.450
Minimum, maximum	2.64, 6.48	3.70, 6.44
T_{max} (day)		
n	15	15
Mean (SD)	13.2476 (5.79905)	9.3792 (3.15047)
CV%	43.77436	33.58986
Geometric mean	11.8357	8.8446
Median	13.9993	9.9757
Minimum, maximum	3.208, 20.999	4.924, 14.194
$T_{1/2}$ (day)		
n	13	15
Mean (SD)	22.249 (7.1629)	21.261 (6.8036)

Parameter (unit) Statistics	CT-P41 (N=15)	EU-approved Prolia (N=15)
CV%	32.1951	31.9997
Geometric mean	21.160	20.243
Median	22.304	22.244
Minimum, maximum	11.27, 34.72	11.13, 37.17
λ_z (1/day)		
n	13	15
Mean (SD)	0.03454 (0.012064)	0.03606 (0.012393)
CV%	34.926714	34.370430
Geometric mean	0.03276	0.03424
Median	0.03108	0.03116
Minimum, maximum	0.0200, 0.0615	0.0186, 0.0623
CL/F (L/day)		
n	13	15
Mean (SD)	0.239 (0.0912)	0.214 (0.0485)
CV%	38.1030	22.7242
Geometric mean	0.229	0.209
Median	0.216	0.208
Minimum, maximum	0.17, 0.52	0.16, 0.32
V_z/F (L)		
n	13	15
Mean (SD)	7.308 (2.2900)	6.276 (1.5120)
CV%	31.3337	24.0902
Geometric mean	6.979	6.099
Median	6.870	6.371
Minimum, maximum	3.94, 11.38	3.86, 9.00

Abbreviations: λ_z, terminal elimination rate constant; $\%AUC_{ext}$, percentage of the area extrapolated for calculation of area under the serum concentration-time curve from time 0 to infinity; $AUC_{0\text{-inf}}$, area under the serum concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the serum concentration-time curve from time 0 to the last quantifiable concentration; CL/F, apparent total body clearance; C_{max}, maximum serum concentration; CV%, percent coefficient of variation; EU, European Union; PK, pharmacokinetic(s); SD, standard deviation; $T_{1/2}$, terminal elimination half-life; T_{max}, time to the maximum serum concentration; V_z/F, apparent volume of distribution during the terminal phase after non-intravenous administration.

Source: Post-text Table 14.2.2.1.

Study CT-P41 1.2 (pivotal PK study)

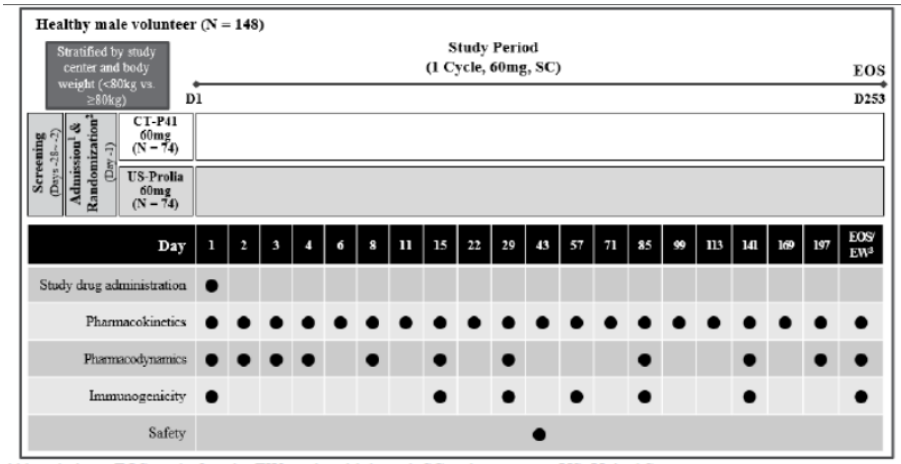
Study design

This study was a phase 1, randomised, double-blind, two-arm, parallel group, single-dose study to compare PK/PD, safety and immunogenicity between CT-P41 and US-licensed Prolia in healthy male subjects.

The study was conducted at two study centres in Korea between 06 Oct 2021 and 20 Oct 2022.

The study included screening (day -28 to day -2), admission (day -1), study period (day 1 to EOS), and end-of-study (EOS) visit (day 253).

The study design in depicted in Figure 2.



Abbreviations: EOS, end of study; EW, early withdrawal; SC, subcutaneous; US, United States

1. Re-check of inclusion and exclusion criteria.
2. Randomization occurred within 24 hours prior to study drug administration once all pertaining tests and assessments for enrollment had been concluded to confirm the eligibility of a subject on Day -1.
3. All EOS assessments occurred on Day 253, and all EW assessments occurred if a subject withdrew prior to EOS visit.

Figure 2. Study design overview

Conduct of the study

The original protocol (version 1.0, dated 10 June 2021) was amended three times as follows:

- Protocol version 1.1 dated 08 July 2021 (following change: exclusion criteria was revised to clarify the use of COVID-19 vaccination during the study).
- Protocol version 1.2 dated 19 July 2021 (following change: added syphilis screening test for screening).
- Protocol version 1.3 dated 22 July 2022 (following changes: Updated contact information of CRO and SAE reporting method, updated the current policy of sample storage and shipment, and clarified that the sample retention was based on the subject's consent on ICF, clarified sentences of statistical analysis methods for PK, PD, safety, and others, added an analytical facility for PD testing).

Study population

Inclusion criteria

1. Healthy male subjects aged between 28 and 55 years (both inclusive) at the screening visit (healthy was defined as no clinically relevant abnormalities identified by investigator' decision based on a detailed medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory tests prior to study drug administration).
2. Subject had a BMI between 18.5 and 29.9 kg/m^2 (both inclusive), and a body weight between 50.0 and 99.9 kg (both inclusive), when rounded to the nearest tenth.
3. Subject with total serum calcium ≥ 8.5 mg/dL (≥ 2.125 mmol/L) and serum 25-OH vitamin D ≥ 20 ng/mL (≥ 50 nmol/L, if vitamin D deficiency had been supplemented with 400-1000 IU daily at the investigator's discretion, and retest result showed the level above 20 ng/mL within the screening period, the subject could be enrolled in the study. The retest was limited up to once within the screening period).
4. Subject was able to understand and to comply with protocol requirements, instructions, and restrictions.

5. Subject was informed and able to understand the full nature and purpose of the study, including possible risks and side effects, and was given ample time and opportunity to read and understand the information provided to him. Subject had the ability and agreed to cooperate with the investigator and signed and dated the written informed consent prior to any of the screening procedures being performed.
6. Male subject and their female partner of childbearing potential agreed to use a highly effective method of contraception for at least 5 months after the study drug administration. A man or his female partner was of childbearing potential if, in the opinion of the investigator, he or she was biologically capable of having children and was sexually active. Male subjects and their female partners who had been surgically sterilised for less than 6 months prior to the date of informed consent agreed to use any medically acceptable methods of contraception.

Exclusion criteria

1. Subject was a female.
2. Subject with a hypersensitivity to any component of denosumab or dry natural rubber (a derivative of latex).
3. Subject was confirmed or suspected with infection of coronavirus disease 2019 (COVID- 19) at screening, or had had contact with COVID-19 patient within 14 days from screening.
4. Subject had a medical history of and/or current medical condition including any of the following(s):
   a) Known risk factors for hypocalcaemia including hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, or receiving dialysis.
   b) Oral or dental conditions including osteomyelitis or osteonecrosis of the jaw; active dental or jaw condition which required oral surgery; planned invasive dental procedure (e.g., tooth extraction, dental implants, oral surgery); unhealed dental oral surgery.
   c) History of any disease that might influence the results of study drug including rheumatoid arthritis, Paget's disease, osteogenesis imperfecta, osteomalacia, ankylosing spondylitis, or fracture within 6 months prior to the study drug administration.
   d) Known intolerance to calcium or vitamin D supplements.
   e) Known infection with active hepatitis B, hepatitis C, human immunodeficiency virus (HIV) or syphilis. However, a subject with past hepatitis B virus was allowed if resolved.
   f) History of systemic or local infection, a known risk for developing sepsis, and/or known active inflammatory process or evidence of an infection requiring inpatient hospitalisation or intravenous antibiotics within 6 months prior to the study drug administration.
   g) Seizures.
   h) Any malignancy.
   i) Any clinically significant cardiac, respiratory, renal, hepatic, gastrointestinal, hematologic, psychiatric disease, or any uncontrolled medical illness at the investigator's discretion.
5. Subject had a history of and/or concurrent use of medications including any prior therapy of the following(s):

   a) Prescription drugs, over-the-counter drugs which could affect the outcome of the study in the opinion of the investigator, dietary supplements, or herbal remedies within 2 weeks or 5 half-lives (whichever was longer) prior to the study drug administration.

   b) Subject had received any biologic agent(s) (including but not limited to monoclonal antibodies or fusion proteins) within 90 days prior to study drug administration or within 5 half-lives (whichever was longer).

c) Subject previously had participated in another clinical trial and received an investigational product within 6 months (180 days) prior to study drug administration or within 5 half-lives of the investigational product (whichever was longer) or planned to participate in another clinical trial during this study.

d) Any therapy that might significantly affect bone metabolism:

- Medications for osteoporosis (e.g., bisphosphonates, calcitonin, parathyroid hormone (or any derivatives), fluoride, strontium)
- Medications including anticonvulsants, systemic glucocorticosteroids (inhaled or topical corticosteroids administered more than 2 weeks prior to the study drug administration were allowed), anabolic steroids (or testosterone), supplemental vitamin D (>1,000 IU/day), calcitriol and available analogues, diuretics within 6 months prior to the study drug administration
- Requiring regular use of medications for calcium supplement at the discretion of investigator

e) Live or live-attenuated vaccine within 4 weeks prior to the study drug administration or planned to do so during the study period. *Note. Any authorised COVID-19 vaccines that are not live or live-attenuated types (e.g., mRNA, viral vector) were allowed during both the screening and study period. However, COVID-19 vaccines were prohibited for 2 weeks prior and after the study drug administration (total of 4 weeks).*

6. Subject was planning to father a child or donate sperms during the study period or within 5 months period following the study drug administration.
7. Subject had reasonable evidence of drug/alcohol/nicotine abuse prior to the study drug administration as follows:

   a) Positive result for urine drug test during screening and/or the opinion of the investigator.

   b) History or presence of regular consumption of alcohol exceeding an average weekly intake of >14 units of alcohol in recent 3 months prior to the study drug administration.

   c) Consumed more than 10 cigarettes or equivalent per day within 4 weeks prior to the study drug administration.
8. Subject was unwilling to avoid the use of alcohol or alcohol-containing foods, medications, or beverages within 24 hours prior to each study visit and/or unable to refrain from smoking during in-house stays.
9. Subject had donated whole blood or lost 450 mL or more blood within 8 weeks (plasma/platelets donation within 4 weeks) prior to the study drug administration and was planning to donate during the study after the study drug administration.
10. Subject had presence of tattoos, sunburn, or other skin disturbances (i.e., cuts, bruises, redness, hardness, tenderness, etc.) on the injection site, which might interfere with a medical assessment of it both prior to and following study drug administration in the opinion of the investigator.
11. Subject was vulnerable (e.g., employees of the clinical trial site or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison or other institutionalised persons by law enforcement).
12. Subject was not likely to complete the study for any reason in the opinion of the investigator including but not limited to the subject showing evidence of a condition (e.g., psychological or

emotional problem, any disorder or resultant therapy) that was likely to invalidate an informed consent or limit the ability of the subject to comply with the protocol requirements.

Treatments

- Test product: CT-P41, 60 mg by SC injection to the upper arm via PFS as a single administration
- Comparator product: US-licensed Prolia, 60 mg by SC injection to the upper arm via PFS as a single administration

All subjects fasted overnight (except water) for at least 8 hours prior to study drug administration. The study drug (a single SC dose of 60 mg denosumab) was administered in subjects to the clean and intact outer upper arm area on the subject's non-dominant side (i.e., left upper arm for a right-hand dominant subject, and vice versa).

Co-administration of Vitamin D

All subjects could take daily supplementation of vitamin D with dose between 400 IU and 1000 IU (both inclusive) at the discretion of the investigator to prevent risk of hypocalcaemia and vitamin D deficiency.

Objectives and endpoints

Primary objective

To demonstrate PK similarity between CT-P41 and US-licensed Prolia in healthy male subjects.

Primary PK endpoints:

- $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max}

Secondary PK endpoints:

- $pAUC_{0\text{-}W16}$, $pAUC_{W16\text{-}inf}$, T_{max}, $T_{1/2}$, $\%AUC_{ext}$, λ_z, CL/F, Vz/F, and MRT

Secondary objective

To evaluate additional PK, PD, safety and immunogenicity of CT-P41 and US-licensed Prolia in healthy male subjects.

Secondary PD endpoints:

- Area under the effect curve (AUEC) of serum type 1 C-telopeptides (s-CTX) over the study period
- Area under the effect curve of procollagen type 1 N-terminal propeptide (P1NP) over the study period
- Percent change from baseline of s-CTX at each study visit
- Percent change from baseline of P1NP at each study visit

PK sampling timepoints:
On day 1 (pre-dose, 6 h and 12 h post-dose), 2, 3, 4, 6, 8, 11, 15, 22, 29, 43, 57, 71, 85, 99, 113, 141, 169, 197, and 253 and in case of early termination.

PD sampling timepoints:
On day 1 (pre-dose), 2, 3, 4, 8, 15, 29, 85, 141, 197 and 253 and in case of early termination.

Secondary safety endpoints:

- Treatment-emergent AEs (TEAEs)
- TE serious AEs (TESAEs)
- TEAEs of special interest (ISR, drug related hypersensitivity/allergic reaction, infection, and hypocalcaemia)
- Hypersensitivity/allergic reaction assessments by vital sign monitoring (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Local site pain using 100 mm VAS
- Vital signs (systolic and diastolic blood pressure, heart rates, respiratory rates, and body temperature)
- Physical examination
- Clinical laboratory tests including haematology, clinical chemistry, and urinalysis
- 12-lead ECG
- Prior and concomitant medications

Immunogenicity

- Incidence of ADA and NAb, and ADA titre

Immunogenicity sampling timepoints:
On day 1 (pre-dose), 15, 29, 57, 85, 141, and 253 and in case of early termination. Subjects were required to fast overnight for 8 hours prior to collect blood samples for PD assessment in the morning.

Sample size
A sample size of 132 subjects (66 subjects in each treatment group) was expected to provide 90% statistical power to show similarity in PK between CT-P41 and US-licensed Prolia using 90% CI approach based on 80% to 125% equivalence margin assuming the expected geometric mean ratio of 1.0 and the CV% of 40%, which was assumed based upon historical PK data. The sample size was calculated from two one-sided tests with each 5% significance level. Approximately 148 subjects (74 in each group) were needed to be enrolled for the anticipated 10% drop-out rate.

Randomisation

The randomised code was generated by a contract research organisation prior to the study. Randomisation occurred within 24 hours prior to Day 1 dosing after all pertaining tests and assessments for enrolment had been concluded to confirm the eligibility of a subject on Day -1. Subjects were randomly assigned to one of the 2 treatment groups in a 1:1 ratio (CT-P41 or US-licensed Prolia). The randomisation was stratified by body weight (<80 kg vs. ⩾80 kg) measured on Day -1 and study centre for balanced distribution.

Statistical methods
All statistical analyses were performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Analysis sets

Intention-to-treat (ITT) set was defined as all subjects successfully screened and randomly assigned to receive a study drug (CT-P41 or US-licensed Prolia), regardless of whether or not any study drug was administered.

PK set was defined as all subjects who received a full dose of study drug (CT-P41 or US-licensed Prolia) and who had at least one post-dose PK result with a concentration above the LLoQ for denosumab.

Analysis of primary PK endpoints

For the primary PK endpoints, statistical analysis of log-transformed primary endpoints ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}) was conducted based on an analysis of covariance (ANCOVA) model with treatment as a fixed effect and body weight on Day -1 and study centre as covariates. Back transformation provided the ratio of geometric least square (LS) mean and 90% CIs for these ratios. The similarity between CT-P41 and US-licensed Prolia in terms of PK was to be concluded if the 90% CIs of the ratios of geometric LS mean for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max} were entirely contained within the equivalence margin of 80% and 125%.

Analysis of safety data

Adverse events (AEs)

All AEs were coded by SOC and PT using MedDRA, version 25.1 and graded for intensity according to NCI CTCAE version 5.0.

For subject incidence summaries, a subject was counted only once within each SOC and within each PT. If a subject reported more than 1 AE within the same SOC and/or PT and/or relationship (if needed), the AE with the highest intensity within each SOC and each PT was included.

Relationship to study drug (unrelated, possible, probable, or definite) were summarised and events were considered related if relationship was possible, probable, or definite. AEs with no relationship or intensity were summarised separately under a missing category. An AE related to COVID-19 was coded with a PT of 'COVID-19' or 'coronavirus infection,' if required.

TEAESs/ TESAEs and deaths/ TEAEs leading to study discontinuation

All above were summarised with the number and percentage of subjects by SOC, PT, relationship, maximum intensity, and treatment group. The total number and percentage of subjects with at least one TEAE or TESAE or TEAE leading to study drug discontinuation were also displayed.

Immunogenicity analysis

For the Safety Set, the number and percentage of subjects with the results of the ADA and NAb were summarised at each scheduled visit by treatment group. The number of subjects with at least one ADA/NAb positive result after the study drug administration including scheduled and unscheduled visits regardless of their ADA status at baseline were presented by treatment group.

The descriptive statistics of ADA titre results for each treatment group were also presented by scheduled visit. All immunogenicity data were listed for each subject by treatment group and visit.

PK results

Summary of subject disposition is depicted in Figure 3.

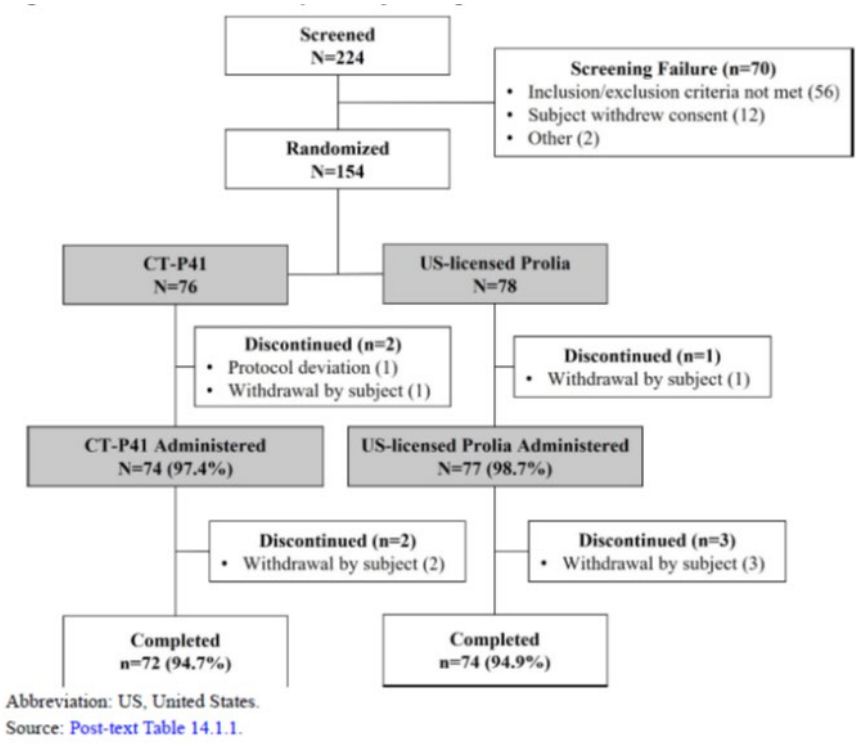


Figure 3. Summary of subject disposition

Co-administration of Vitamin D

All 151 subjects took vitamin D 1000 IU every day until the end of the study. One subject in the US-licensed Prolia treatment group skipped vitamin D for 3 days during the study but completed the supplementation until the end of the study after that.

Protocol deviations

One subject in the CT-P41 treatment group had a major protocol deviation. The subject was initially randomised with a first Subject ID and withdrew the consent of study participation before study drug administration. After the withdrawal, the subject re-entered the study with a second Subject ID for rescreening. According to the protocol, rescreening was only allowed for screen failed subjects. The deviation was reported from the site after study drug administration. During the blinded DRM, it was discussed to exclude the data for the first Subject ID, which were collected only during the screening visit, to avoid redundant summarisation with duplicated information from 2 subject IDs for 1 subject. Therefore, only the second Subject ID remained in the study and was included in all analysis set as there were no other factors that would compromise the analysis of the data collected from the second subject ID.

Exclusion criteria violation (COVID-19 vaccination) occurred in one subject in the US-licensed Prolia treatment group and one subject in the CT-P41 treatment group after randomisation. The deviations were reviewed and determined not to have significant impact on the study results. Therefore, they were not considered as major protocol deviations.

The PK set included a total of 151 subjects (all of the subjects were non-Hispanic or non-Latino Asian males. Age of subjects ranged from 28 to 55 years with a median age of 38 years. The overall mean (SD) of body weight and BMI at screening was 75.78 (9.94) kg and 24.80 (2.60) kg/m^2, respectively.

Among 151 subjects in the PK Set (74 and 77 subjects in the CT-P41 and US-licensed Prolia treatment groups, respectively), 2 subjects (both in the US-licensed Prolia treatment group) who early discontinued from the study on Day 8 and Day 11, respectively, were not included in the analysis of $AUC_{0\text{-inf}}$ due to insufficient sampling for calculation of λ_z. On top of the 2 subjects, 3 additional early withdrawal subjects (2 and 1 subjects in the CT-P41 and US-licensed Prolia treatment groups, respectively) were excluded from the analysis of $AUC_{0\text{-last}}$. The 5 early withdrawal subjects would provide $AUC_{0\text{-last}}$ only up to the last quantifiable sampling time point earlier than EOS, which yield $AUC_{0\text{-last}}$ values less than when they would have completed the PK sampling until EOS. Overall, total of 149 subjects and 146 subjects were included in the analysis of $AUC_{0\text{-inf}}$ and $AUC_{0\text{-last}}$, respectively.

The geometric LS means of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max} were similar between the 2 treatment groups (see Table 5). The 90% CIs for the ratio of geometric LS means were within the equivalence margin of 80% to 125% for all 3 primary endpoints, indicating the similarity between CT-P41 and US-licensed Prolia in terms of PK.

Table 5. Statistical analysis of primary PK parameters (ANCOVA): PK set

Parameter (unit) Statistics	CT-P41 (N=74)	US-licensed Prolia (N=77)
$AUC_{0\text{-inf}}$ (day•µg/mL)		
n	74	75
Geometric LS Mean	319.425	297.741
Ratio of Geometric LS Means	107.28	
90% CI for Ratio of Geometric LS Means	[100.39, 114.65]	
$AUC_{0\text{-last}}$ (day•µg/mL)		
n	72	74
Geometric LS Mean	313.836	293.682
Ratio of Geometric LS Means	106.86	
90% CI for Ratio of Geometric LS Means	[99.92, 114.28]	
C_{max} (µg/mL)		
n	74	77
Geometric LS Mean	5.521	5.461
Ratio of Geometric LS Means	101.09	
90% CI for Ratio of Geometric LS Means	[95.20, 107.34]	

Abbreviations: ANCOVA, analysis of covariance; $AUC_{0\text{-inf}}$, area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the concentration-time curve from time 0 to the last quantifiable concentration; C_{max}, maximum serum concentration; CI, confidence interval; LS, least square; PK, pharmacokinetic; US, United States.

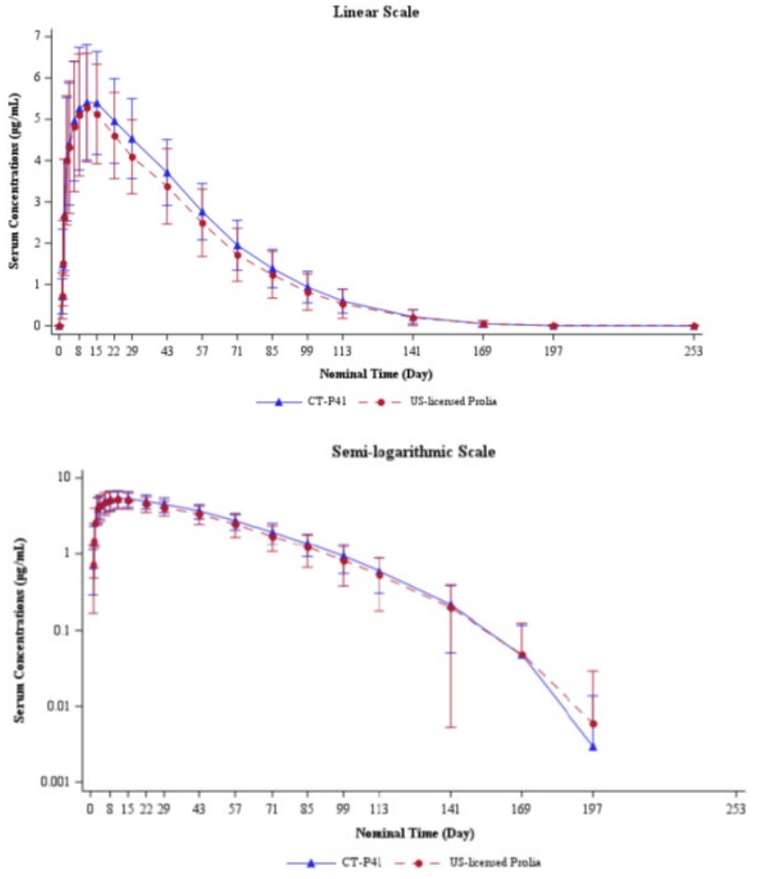
Note: An analysis of covariance (ANCOVA) was performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect, and stratification factors (body weight as measured on Day -1 and study center) as covariates.

$AUC_{0\text{-last}}$ from early withdrawal subjects were not included. $AUC_{0\text{-inf}}$ values were not included if adjusted $R^2 < 0.85$ or not meeting a minimum of three PK concentration data points (excluding C_{max}) used in the calculation of λ_z.

Source: Post-text Table 14.2.1.4.

Mean (±SD) serum concentrations of denosumab were observed until Day 253 following a single administration of CT-P41 (60 mg) or US-licensed Prolia (60 mg) (see Figure 4). After sharp increase up to Day 11, the mean serum concentration gradually decreased until reaching approximately 1 µg/mL. After Day 113 (Week 16), the PK profile in both treatment groups clearly displayed faster decline in serum concentrations with steeper slope indicating a change in PK characteristics (semi-logarithmic scale). The serum denosumab concentrations in both treatment groups started to reach a level very close to 0 µg/mL on Day 169, and all subjects had 0 µg/mL of serum concentration on Day 253 (EOS).

The overall PK profile of the CT-P41 treatment group was similar to the US-licensed Prolia treatment group.



Abbreviations: PK, pharmacokinetic; SD, standard deviation; US, United States.
Note: Concentrations below the lower limit of quantification (BLQ) were dealt with the rules described in the SAP.
Source: Post-text Figure 14.2.1.1.

Figure 4. Mean (±SD) serum concentrations of denosumab versus time by treatment group (linear and semi-logarithmic scales): PK set

The means [CV%] of $pAUC_{0\text{-}W16}$ and $pAUC_{W16\text{-}inf}$ were comparable between the 2 treatment groups. The median [range] of T_{max} in the CT-P41 treatment group was very similar to that of US-licensed Prolia treatment group. The mean [CV%] of $t_{1/2}$ in the CT-P41 treatment group was similar to that of US-licensed Prolia treatment group. The means of $\%AUC_{ext}$, λ_z, CL/F, Vz/F, and MRT were comparable between the 2 treatment groups.

Table 6. Secondary PK parameters of denosumab by treatment group: PK set

Parameter (unit) Statistics	CT-P41 (N=74)	US-licensed Prolia (N=77)
CV%	46.774058	47.691871
Geometric mean	10.98310	9.60331
$T_{1/2}$ (day)		
n	74	75
Mean (SD)	16.79421 (4.663848)	16.21354 (4.626789)
Median	16.57280	16.24758
Min, max	8.1434, 37.1104	6.5227, 30.6573
CV%	27.770573	28.536581
Geometric mean	16.19533	15.54767
$\%AUC_{ext}$ (%)		
n	74	75
Mean (SD)	1.08125 (2.139895)	0.83060 (0.763516)
Median	0.67715	0.65961
Min, max	0.1361, 14.7365	0.0982, 4.7924
CV%	197.910143	91.923068
Geometric mean	0.61503	0.56555
λ_z (1/day)		
n	74	75
Mean (SD)	0.04442 (0.012712)	0.04667 (0.015195)
Median	0.04182	0.04266
Min, max	0.0187, 0.0851	0.0226, 0.1063
CV%	28.615416	32.558610
Geometric mean	0.04280	0.04458
CL/F (L/day)		
n	74	75
Mean (SD)	0.19223 (0.065118)	0.21740 (0.096612)
Median	0.17664	0.19104
Min, max	0.1094, 0.5602	0.1043, 0.8203
CV%	33.874575	44.439114
Geometric mean	0.18438	0.20395
V_z/F (L)		
n	74	75
Mean (SD)	4.42176 (1.053691)	4.75276 (1.339845)
Median	4.09188	4.47435
Min, max	2.7345, 7.8080	2.4870, 9.1392
CV%	23.829677	28.190869
Geometric mean	4.30792	4.57471
MRT (day)		
n	74	75
Mean (SD)	43.22873 (5.546940)	41.61850 (6.823782)
Median	43.33697	42.73058
Min, max	29.8285, 60.8905	27.4392, 58.1773
CV%	12.831606	16.396032
Geometric mean	42.87273	41.04785

Parameter (unit) Statistics	CT-P41 (N=74)	US-licensed Prolia (N=77)
$pAUC_{0\text{-}W16}$ (day•µg/mL)		
n	74	75
Mean (SD)	320.06720 (73.021046)	294.36436 (80.161089)
Median	328.29779	300.09364
Min, max	106.7986, 467.6843	73.0864, 538.4920
CV%	22.814286	27.231928
Geometric mean	310.67166	281.98665
$pAUC_{W16\text{-}inf}$ (day•µg/mL)		
n	74	75
Mean (SD)	16.58859 (12.754355)	14.67749 (12.712211)
Median	13.69687	11.81347
Min, max	0.3021, 80.9119	0.0607, 55.3823
CV%	76.886324	86.610271
Geometric mean	11.86892	8.25848
T_{max} (day)		
n	74	77
Mean (SD)	12.19493 (5.704065)	10.85161 (5.175338)
Median	10.02951	10.01250
Min, max	1.9965, 28.0444	1.9410, 28.0014

Abbreviations: λz, terminal elimination rate constant; %AUCext, percentage of the area extrapolated for calculation of area under the concentration-time curve from time 0 to infinity; $pAUC_{0\text{-}W16}$, partial area under the concentration-time curve from time 0 to Week 16; $pAUC_{W16\text{-}inf}$, partial area under the concentration-time curve from Week 16 to infinity; CL/F, apparent total body clearance; CV%, percent coefficient of variation; MRT, mean residence time; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, terminal half-life; T_{max}, time of observed maximum serum concentration; US, United States; Vz/F, apparent volume of distribution during the terminal phase.

PK in target population

Study CT-P41 3.1 (Comparative efficacy and safety study)

This study was a phase 3, double-blind, randomised, active-controlled, parallel group study to compare efficacy, PK/PD and safety of CT-P41 and US-Prolia in postmenopausal women with osteoporosis.

Patients received an initial dose of 60 mg of CT-P41 or US-licensed Prolia on Day 1 (Week 0), followed by the study drug on Week 26 during Treatment Period I, and then at Week 52 during Treatment Period II as per the second randomisation.

A secondary endpoint of this study was to evaluate the serum concentration and PK parameters of denosumab after administration of CT-P41 and US-licensed Prolia.

The design and methods of the study are presented in Section 2.5.5 "Clinical Efficacy".

The following PK parameter was assessed up to Week 78:

- Trough serum concentration (C_{trough}) (concentration prior to the next study drug administration)

The following PK parameters were assessed over the first 26 weeks:

- C_{max} after the first administration of study drug,
- Truncated area under the concentration-time curve from zero to Week 26 ($AUC_{0\text{-}t}$),
- T_{max} of Denosumab after the first administration of the study drug,
- Volume of distribution (Vd) and
- $T_{1/2}$

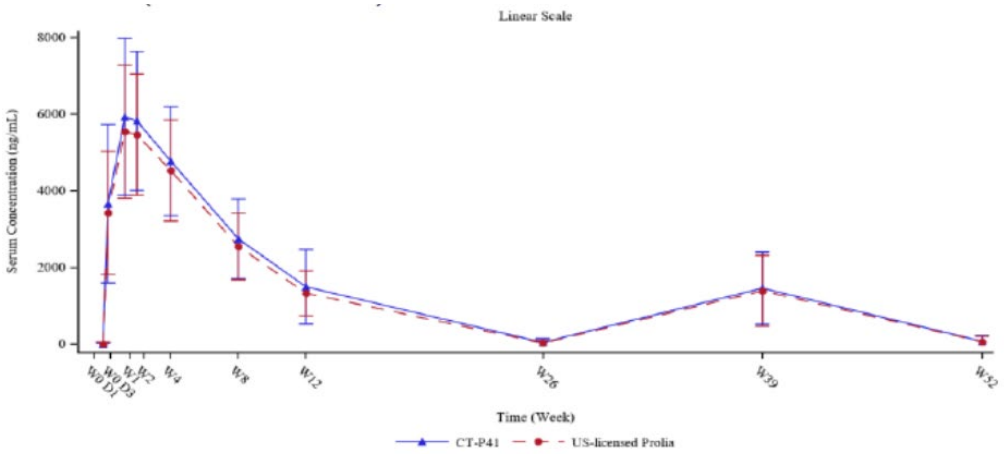
PK results

Denosumab serum concentration data

Treatment period I

In Treatment Period I, the serum concentration observed until Week 52 was generally comparable between the CT-P41 and US-licensed Prolia groups (see Figure 5). After the first study drug administration at Week 0 (Day 1), the mean serum concentration sharply increased up to Week 1 and gradually decreased until Week 26 in the CT-P41 and US-licensed Prolia groups. After the study drug administration at Week 26, the PK profile in both groups also displayed increase up to Week 39, followed by decrease until Week 52 (prior to the study drug administration at Week 52).

The overall trend of PK profile in the levels of serum concentration up to Week 52 was similar between the CT-P41 and US-licensed Prolia groups.



Abbreviations: D, Day; LLoQ, lower limit of quantification; PK, pharmacokinetic; SD, standard deviation; US, United States; W, Week.
Note: Serum concentration below the LLoQ were set to 0. Only positive values of mean (± SD) were displayed.
Source: Post-text Figure 14.2.1.1

Figure 5. Mean (±SD) PK serum concentrations of denosumab (Treatment period I): PK set

Treatment period II

In Treatment Period II, the serum concentration observed until Week 78 (EOS) was generally comparable among the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups (see Figure 6 and Table 7). After the study drug administration at Week 52, the mean serum concentration increased up to Week 60 and subsequently decreased until Week 78 in the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups. The overall trend in increasing and decreasing levels of serum concentration was similar among the 3 groups up to Week 78, which indicated that PK profiles after a single transition at Week 52, from US-licensed Prolia to CT-P41, were not different from those maintained on US-licensed Prolia. At Week 78, the mean serum concentration in the switched to CT-P41 group was higher compared to the CT-P41 maintenance and US-licensed Prolia maintenance groups because the serum concentration for 1 patient in the switched to CT-P41 group was 4900 ng/mL at Week 78 which was increased from the serum concentration of 1010 ng/mL at Week 68. Even though the patient had high serum concentration at Week 78, the median serum concentration of Week 78 for all 3 groups was 0 ng/mL.

It was also confirmed by the bioanalytical laboratory that no sample issue was observed for this patient.

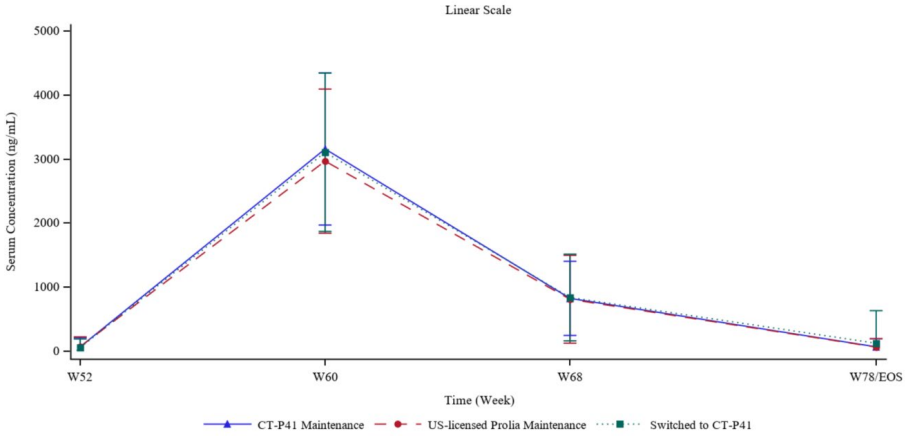


Figure 6. Mean (± SD) PK serum concentrations of denosumab (Treatment period II): PK-treatment period II subset

Table 7. Descriptive statistics of PK serum concentrations of denosumab (ng/ml) (Treatment period II): PK-treatment period II subset

Visit Statistic	CT-P41 Maintenance (N=218)	US-licensed Prolia Maintenance (N=97)	Switched to CT-P41 (N=100)
Week 60			
n	217	95	99
Mean (SD)	3158.28 (1187.375)	2968.36 (1124.176)	3106.78 (1235.172)
Median	3110.00	2850.00	3000.00
Min, Max	244.0, 5990.0	24.2, 5750.0	0, 6910.0
Week 68			
n	215	96	100
Mean (SD)	826.64 (578.146)	812.81 (685.951)	840.06 (675.986)
Median	760.00	663.00	673.50
Min, Max	0, 2640.0	0, 4980.0	0, 4590.0
Week 78			
n	214	96	98
Mean (SD)	70.24 (126.852)	66.60 (129.573)	126.15 (508.689)
Median	0	0	0
Min, Max	0, 707.0	0, 584.0	0, 4900.0

Abbreviations: LLoQ, lower limit of quantification; Max, maximum; Min, minimum; PK, pharmacokinetic; SD, standard deviation; US, United States.
Note: Serum concentration below the LLoQ was set to 0 in the summary.
Source: Post-text Table 14.2.7.1

PK parameters of denosumab

Treatment period I

In Treatment Period I, the C_{trough} of denosumab at Weeks 0 and 26 were assessed as the serum concentration at Weeks 26 and 52 prior to the study drug administration, respectively (see Table 8). The C_{max}, AUC_{0-t}, T_{max}, Vd, and $T_{1/2}$ were assessed after the first study drug administration at Week 0 (Day 1) over 26 weeks. The PK parameters results were generally similar between the CT-P41 and US-licensed Prolia groups.

Table 8. Descriptive statistics of PK parameters of denosumab (Treatment period I): PK set

n	237	236
Mean (SD)	6158.9 (1985.17)	5767.2 (1716.20)
Geometric mean (90% CI)	5851.2 (5650.8, 6058.6)	5492.7 (5302.6, 5689.7)
Min, Max	2300, 12300	1040, 10400
AUC_{0-t} (day*ng/mL)		
n	234	232
Mean (SD)	386032.6781 (137545.12393)	357072.0011 (114838.97632)
Min, Max	105224.420, 1042077.677	73637.767, 728439.893
T_{max} (day)		
n	237	236
Mean (SD)	13.1878 (7.44029)	12.3275 (4.71351)
Min, Max	1.943, 84.984	2.140, 29.907
V_d (L)		
n	217	221
Mean (SD)	7.0040 (2.46385)	7.6586 (3.43354)
Min, Max	2.881, 14.364	2.502, 33.665
$T_{1/2}$ (day)		
n	217	221
Mean (SD)	28.3206 (6.55464)	28.5531 (8.16868)
Min, Max	11.587, 54.650	12.158, 97.973

Abbreviations: AUC_{0-t}, truncated area under the concentration-time curve from zero to Week 26; CI, confidence interval; C_{trough}, trough serum concentration; C_{max}, maximum serum concentration after the first administration of the study drug; LLoQ, lower limit of quantification; Max, maximum; Min, minimum; NC, not calculated; PK, pharmacokinetic; SD, standard deviation; T_{max}, time of observed maximum serum concentration of denosumab after the first administration of the study drug; $T_{1/2}$, terminal elimination half-life over the first 26 weeks; US, United States; V_d, volume of distribution over the first 26 weeks.
Note: Serum concentration below the LLoQ was set to 0 in the summary. The 90% CI of geometric mean was summarized for C_{trough} and C_{max} only. For log-transformed C_{trough} and C_{max}, the 90% CI of mean was calculated using t-distribution and back-transformed to original scales.
Source: Post-text Table 14.2.7.2.

Treatment period II

One patient in the switched to CT-P41 group reported high serum concentration (4900 ng/mL) at Week 78, and it affected the mean C_{trough} of the switched to CT-P41 group at Week 52 (the serum concentration of Week 78) which was higher compared to the results from the CT-P41 maintenance and US-licensed Prolia maintenance groups (see Table 7). Even though the patient had high serum concentration at Week 78, the median C_{trough} for all 3 groups was 0 ng/mL. There was a large variability observed in C_{trough} at Week 52 but considering the patient with high serum concentration, the result of C_{trough} was generally similar among the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups.

After the study drug administration at Week 52, the C_{trough} was well maintained even after switching from US-licensed Prolia to CT-P41.

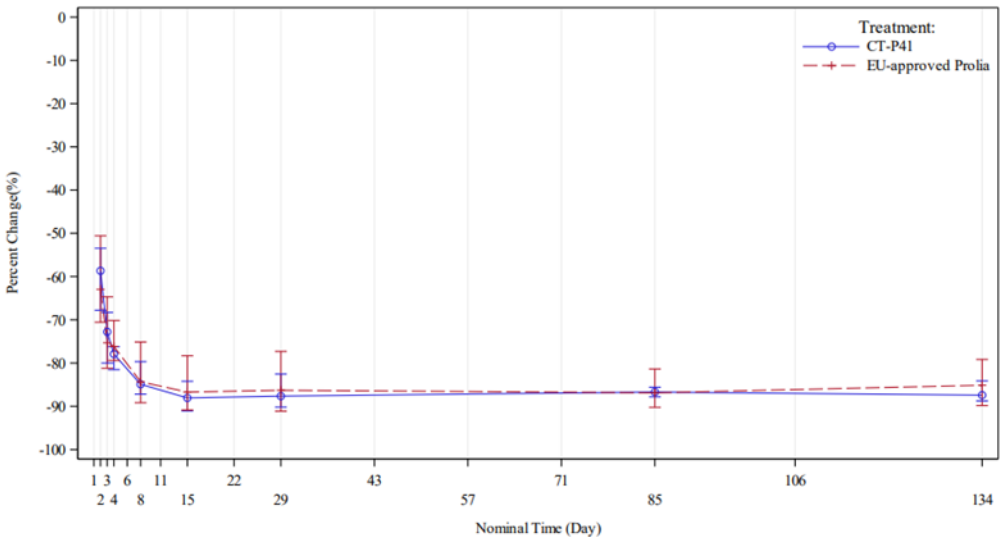
2.5.2.2. Pharmacodynamics

In the pharmacodynamic (PD) studies, serum concentrations of the following PD markers were determined: the bone catabolism biomarker, serum cross-linked C-telopeptide of type I collagen (CTX), and the bone anabolism biomarker, total procollagen type 1 N-terminal propeptide (P1NP). When bone resorption is enhanced, as in osteoporosis, type I collagen is degraded to an increased extent, leading to an increased level of collagen in blood circulation. Relevant collagen type I fragments include the C-terminal telopeptides, in which the α-aspartic acid present in the molecule converts to the β-form of aspartic acid (β-CTx). These isomerised telopeptides are specific for the degradation of type I collagen

dominant in bone. Unlike CTX, which is a catabolic bone turnover marker, procollagen type I N-propeptide (P1NP) is anabolic marker. Procollagen I molecule is synthesised by osteoblasts, and the pro-peptide extensions at the amino- and carboxy-terminals (PINP and PICP respectively) of the procollagen molecule are cleaved off and released into circulation, when collagen molecule is laid down to form the osteoid matrix during bone formation. Bone markers are used for investigating therapeutic response to treatments, since they respond to intervention more rapidly than techniques such bone mineral density. Resorption markers (such as S-CTX) respond in approximately 1 to 3 months after intervention; whereas markers of bone formation, such as S-P1NP, respond later, within 6 to 9 months.

Study CT-P41 1.1

Study CT-P41 1.1 was conducted in healthy male subjects (randomised 32, included 30: 15 subjects in each group: CT-P41 and EU-Prolia). Descriptive data on median percent changes of s-CTX concentration from baseline by treatment group are presented for the PD population shown in the figure below.

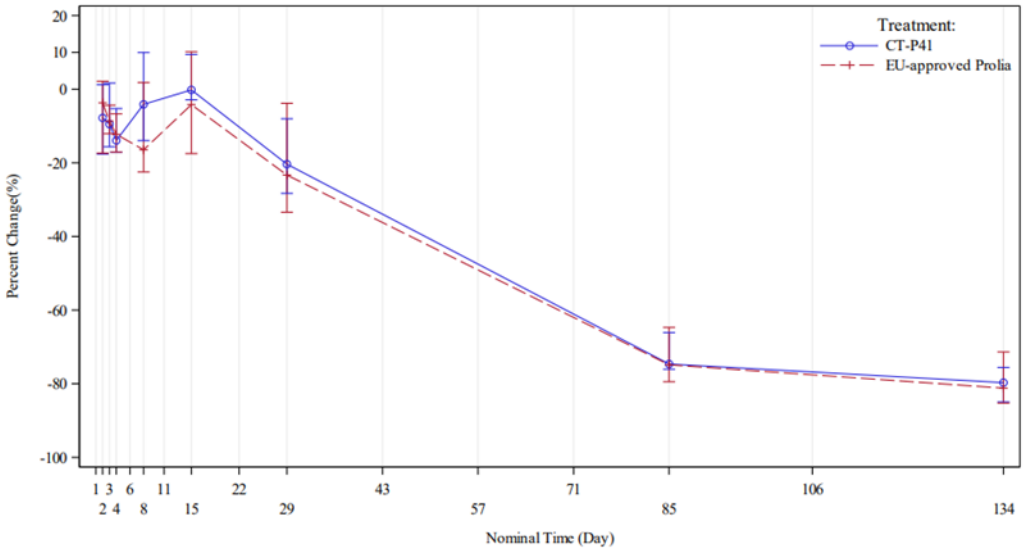


Abbreviations: EU, European Union; PD, Pharmacodynamic(s).

Figure 7. Median percent change from baseline for serum concentration versus time profiles of CTX (PD population)

Median percent changes of P1NP concentration from baseline by treatment group are presented for the PD population in the figure below.

Figure 8. Median percent change from baseline for serum concentration versus time profiles of P1NP (PD population)



Abbreviations: EU, European Union; PD, Pharmacodynamic(s).

Study CT-P41 1.2

Study CT-P41 1.2 was conducted in 154 healthy male volunteers randomised 1:1 (76 subjects in CT-P41 group and 78 in US-Prolia group).

- Secondary PD endpoint (area under the effect curve (AUEC) of serum type 1 C-telopeptide (s-CTX) and procollagen type 1 N-terminal propeptide (P1NP) over the study period)
-

The secondary PD endpoint outcome is summarised for the PD set in Table 9.

Table 9. Summary of PD parameters and statistical analysis of PD parameters (ANCOVA) of denosumab in study CT-P41 1.2: PD set

Parameter (unit)	Statistics	CT-P41 (N=74)	US-Prolia (N=77)
Summary of PD Parameters			
AUEC of s-CTX (day*% Inhibition)	n	71[1]	74[2]
	Mean (SD)	19294.86064 (2406.008095)	18955.13386 (2236.422289)
	CV%	12.469684	11.798504
	GM	19114.22797	18806.69905
	Median	19834.39370	19300.21330
	Q1, Q3	18199.70030, 20716.25400	17662.76890, 20324.07190
	Min, Max	8633.7260, 22785.6988	10211.5004, 22568.7725
AUEC of P1NP (day*% Inhibition)	n	71[1]	74[2]
	Mean (SD)	12351.71836 (2994.360711)	12822.23390 (2218.327113)
	CV%	24.242463	17.300629
	GM	11600.76058	12610.35129
	Median	12707.14430	13150.28555
	Q1, Q3	11266.90410, 14533.18910	11280.26140, 14470.73080
	Min, Max	464.0103, 16043.7482	6502.3350, 16649.7972
Statistical Analysis of PD Parameters			
AUEC of s-CTX (day*% Inhibition)	Geometric LS Mean	19086.422	18832.986
	Ratio of Geometric LS Mean	101.35	
	95% CI for Ratio of Geometric LS Mean	[97.19, 105.68]	
AUEC of P1NP (day*% Inhibition)	Geometric LS Mean	11687.551	12520.491
	Ratio of Geometric LS Mean	93.35	
	95% CI for Ratio of Geometric LS Mean	[83.55, 104.29]	

Sources: CSR CT-P41 1.2 Post-text Tables 14.2.2.2 and 14.2.2.3
Note: An ANCOVA was performed with the natural log-transformed PD parameters as the dependent variable, treatment as a fixed effect and age and baseline value of s-CTX or P1NP as covariates.
N is the number of subjects in the PD Set and n is the number of subjects who contributed to summary statistics.
[1] Three subjects in the CT-P41 group were excluded due to missing baseline for 1 subject and early withdrawal for 2 subjects.
[2] Three subjects in the US-Prolia group were excluded due to early withdrawal.
Abbreviations: ANCOVA, analysis of covariance, AUEC, area under the effect curve; CV%, percent of coefficient of variation; GM, geometric mean; LS, least squares; Max, maximum; Min, minimum; P1NP, procollagen type 1 N-terminal propeptide; PD, pharmacodynamics; Q1, lower quartile; Q3, upper quartile; s-CTX, serum type 1 C-telopeptides; SD, standard deviation

- Secondary endpoint (percent change from baseline of s-CTX and P1NP at each study visit)

Percent change from baseline for serum concentrations of s-CTX and P1NP are summarised by treatment group in Figure 9.

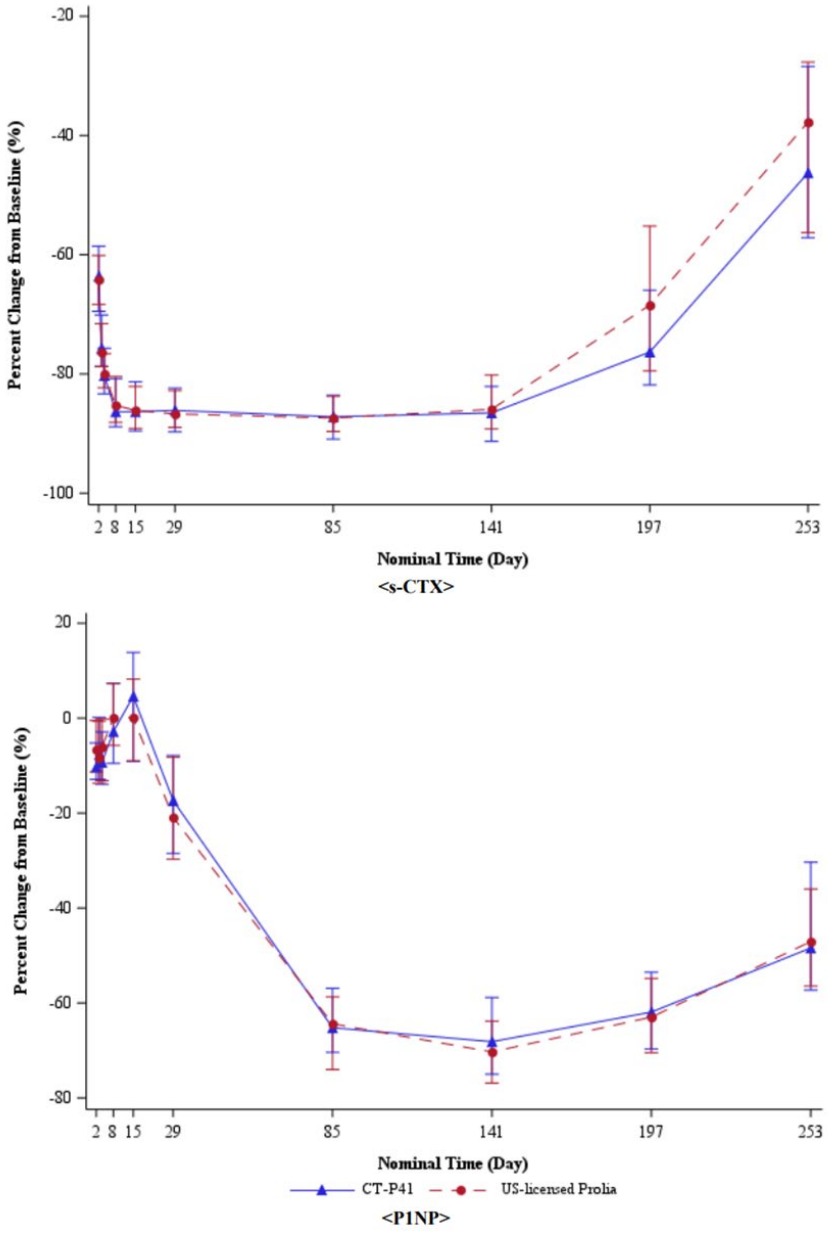


Figure 9. Median (Q1, Q3) Percent Change from Baseline for s-CTX and P1NP Serum Concentrations in Study CT-P41 1.2: PD Set

CT-P41 3.1 study

Phase 3 study CT-P41 3.1 was conducted in 477 women with postmenopausal osteoporosis randomised 1:1 (239 subjects in CT-P41 group and 238 in US-Prolia group). The PD endpoint AUEC of s-CTX was co-primary to primary efficacy endpoint.

The primary PD endpoint outcome is summarised for the FAS in Table 10.

Table 10. Area under the effect curve of s-CTX (day*%) over the initial 6 months (ANCOVA): FAS

Group	n/N[1]	Geometric LS Mean	Geometric LS Mean Ratio[2]	95% CI of Geometric LS Mean Ratio[2]
CT-P41	227 / 239	13835.3915	94.94	(90.75, 99.32)
US-licensed Prolia	221 / 238	14572.6010		

Abbreviations: ANCOVA, analysis of covariate; AUEC, area under the effect curve; BMD, bone mass density; CI, confidence interval; FAS, full analysis set; LS, least squares; s-CTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; US, United States.

Note: An ANCOVA was performed with the natural log-transformed AUEC of s-CTX as the dependent variable, treatment as a fixed effect and age, baseline BMD T-score at the lumbar spine, prior bisphosphonates therapy (Yes versus No), and baseline s-CTX level as covariates.

1. The number of patients who had the result of AUEC of s-CTX / The number of patients in FAS.
2. Geometric LS mean ratio and 95% CI of the ratio, which were obtained from exponentiating the LS mean difference and 95% CI for the difference.

The results for the AUEC of s-CTX and P1NP over the initial 6 months (from Day 1 predose to Week 26 predose) for the PD Set are presented using descriptive statistics are summarised in Table 11 below.

Table 11. Descriptive statistics of AUEC of s-CTX and P1NP over the initial 6 months: PD set

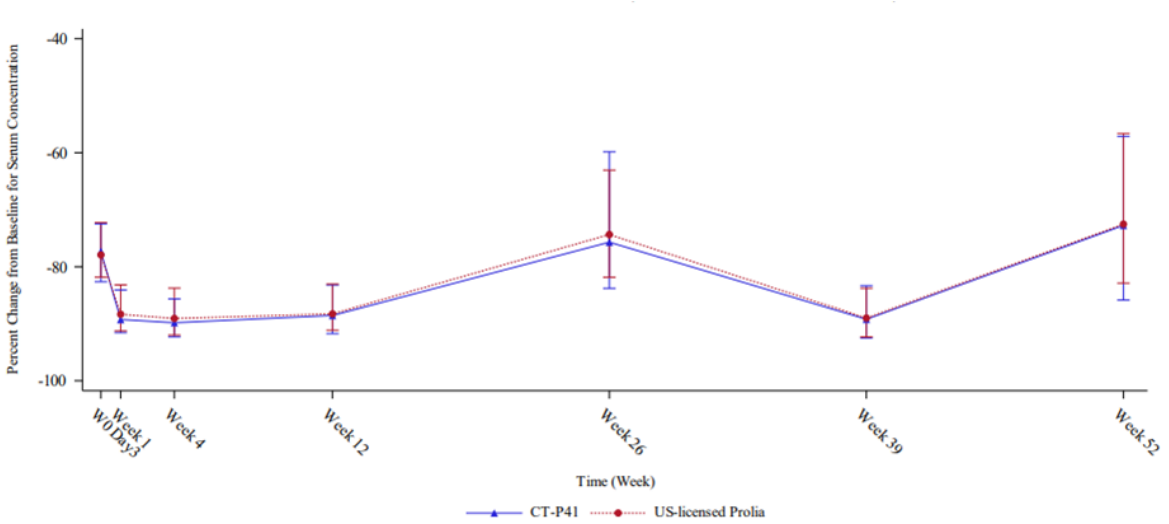
Parameter Statistic	CT-P41 (N=237)	US-licensed Prolia (N=236)
AUEC of s-CTX (day*%)		
n	227	221
Mean (SD)	14603.5726 (2869.78700)	14871.2730 (2158.17748)
Geometric mean	14059.2621	14658.8996
Coefficient of variation (%)	19.6513	14.5124
Median	15383.4768	15475.7958
Min, Max	1106.038, 21301.133	4590.460, 21479.135
AUEC of P1NP (day*%)		
n	227	221
Mean (SD)	9178.4183 (2601.07546)	9307.5439 (2207.93088)
Geometric LS mean	7663.9224	9119.7908
Geometric LS mean ratio (95% CI)[1]	84.04 (73.23, 96.43)	
Coefficient of variation (%)	28.3390	23.7219
Median	9776.3557	9776.3180
Min, Max	1.889, 15763.606	263.625, 14202.070

Abbreviations: ANCOVA, analysis of covariance; AUEC, area under the effect curve; CI, confidence interval; LLoQ, lower limit of quantification; LS, least squares; PD, pharmacodynamic; P1NP, procollagen type 1 N-terminal propeptide; s-CTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; ULoQ, upper limit of quantification; US, United States.

Note: Serum concentration below the LLoQ was set to the LLoQ and the value above the ULoQ was set to the ULoQ in the PD parameter estimation.

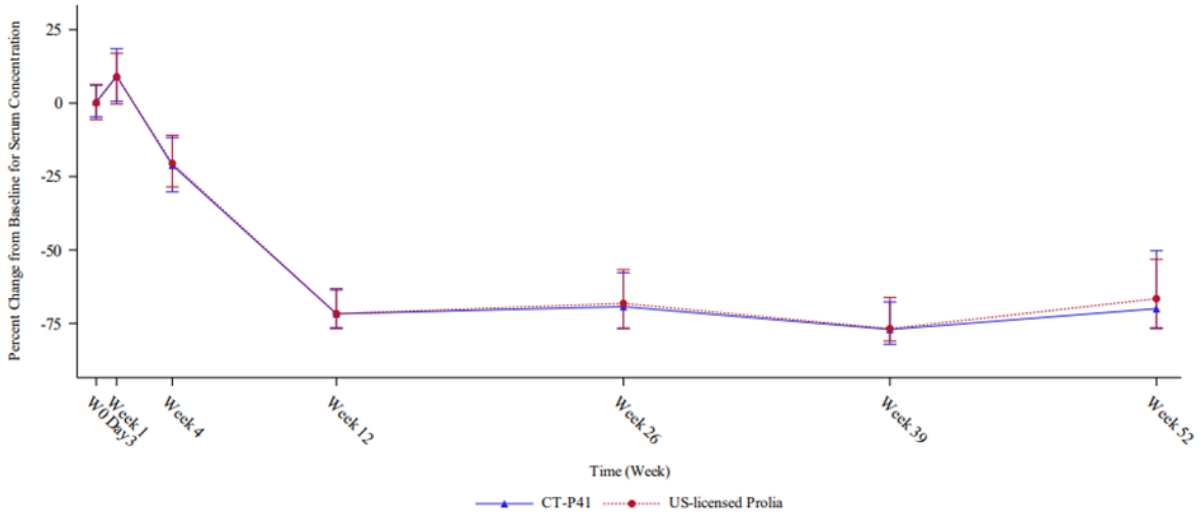
1. Geometric LS mean ratio and 95% CI of the ratio, which were obtained from exponentiating the LS mean difference and 95% CI for the difference using ANCOVA with natural log-transformed AUEC of P1NP as a dependent variable, treatment as a fixed effect and age, baseline BMD T-score at the lumbar spine, prior bisphosphonates therapy (Yes versus No), and baseline P1NP level as covariates.

Plot for the median (Q1, Q3) of percent change from baseline for PD serum concentrations of s-CTX and P1NP for the Treatment Period I (PD Set) and the Treatment Period II (PD-Treatment Period II Subset) are presented in figures below.



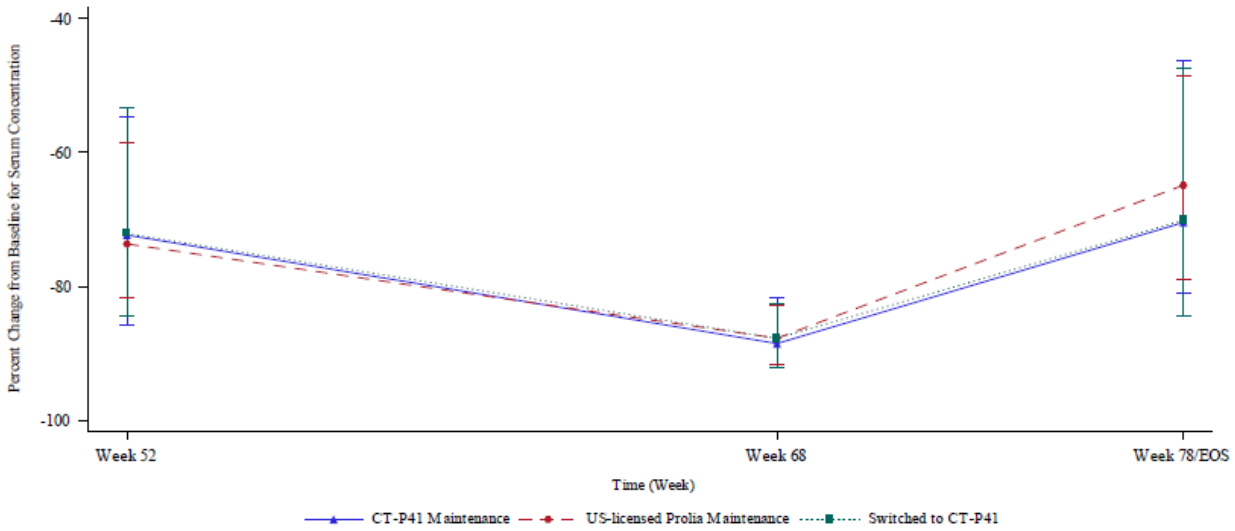
Abbreviations: s-CTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; PD, pharmacodynamic; Q1, the first quartile; Q3, the third quartile; US, United States.

Figure 10. Median (Q1, Q3) of percent change from baseline for pharmacodynamic serum concentrations of s-CTX (treatment period I): PD set



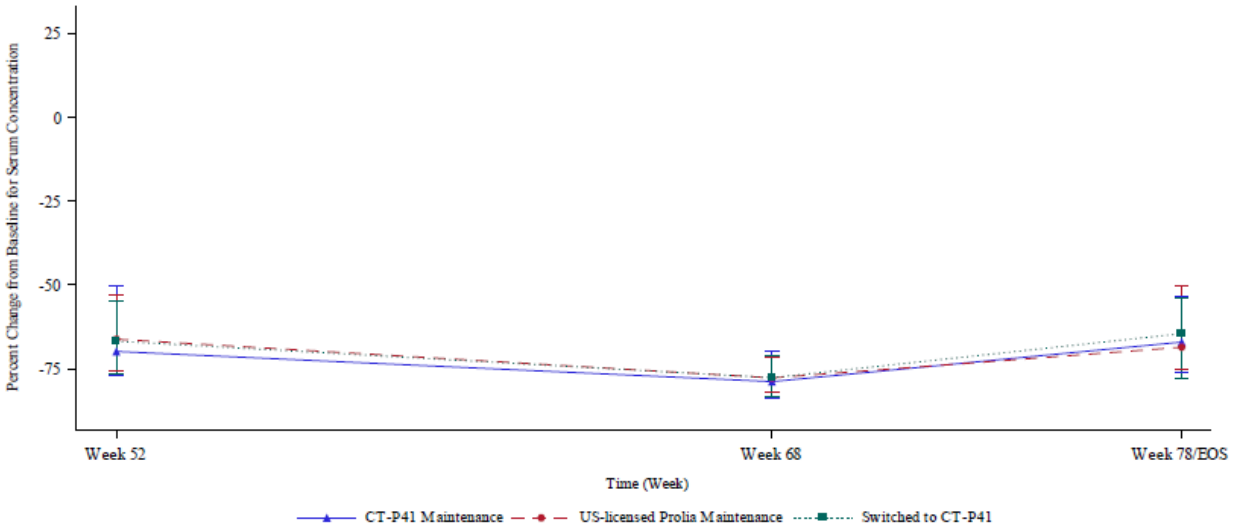
Abbreviations: P1NP, procollagen type 1 N-terminal propeptide; PD, pharmacodynamic; Q1, the first quartile; Q3, the third quartile; US, United States.

Figure 11. Median (Q1, Q3) of percent change from baseline for pharmacodynamic serum concentrations of P1NP (treatment period I): PD set



Abbreviations: s-CTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; PD, pharmacodynamic; Q1, the first quartile; Q3, the third quartile; US, United States.
Source: Post-text Figure 14.2.2.1.

Figure 12. Median (Q1, Q3) of percent change from baseline for pharmacodynamic serum concentrations of s-CTX (treatment period II): PD-treatment period II subset



Abbreviations: P1NP, procollagen type 1 N-terminal propeptide; PD, pharmacodynamic; Q1, the first quartile; Q3, the third quartile; US, United States.
Source: Post-text Figure 14.2.2.1.

Figure 13. Median (Q1, Q3) of percent change from baseline for pharmacodynamic serum concentrations of P1NP (treatment period II): PD-treatment period II subset

2.5.2.3. Immunogenicity

Bioanalytical methods for determination of anti-drug antibodies (ADA) and neutralising antibodies (NAb) are assessed in Section 2.5.2.3 of this AR.

Immunological events in Study CT-P41 3.1 are assessed in Section 2.5.8.3 of this AR.

Study CT-P41 1.1

All subjects in both groups were ADA negative at baseline prior to study drug administration. The proportion of subjects with post-treatment positive ADA result increased during the study in both study groups and peaked at Day 57, when 13/15 subjects in the CT-P41 group and 15/15 in the EU-Prolia group were ADA-positive. Thereafter, some subjects changed back to ADA negative, with 12 ADA-positive subjects in both groups at end of the study. During the course of study, 14/15 (93.3%) in the CT-P41 group and 15/15 (100%) in the EU-Prolia groups had at least one positive ADA result.

The majority of ADA titres were the lowest value of 100 or 300 in both treatment groups (data not shown for brevity). In addition, of the subjects with positive ADA results, only 1 subject (6.7%) in the CT-P41 treatment group and none in the EU-Prolia group had a positive NAb result on Day 85; and this subject was NAb negative again at EOS visit.

There were no TEAEs classified as hypersensitivity/allergic reaction in this study.

Study CT-P41 1.2

One subject in the CT-P41 group was ADA positive (and NAb negative) already prior to study drug administration. Over the course of the study, a great majority of subjects turned ADA positive. The proportion of subjects with positive ADA peaked on Day 85 and were similar between the 2 treatment groups (72/74 [97.3%] and 73/77 [94.8%] subjects in the CT-P41 and US-Prolia treatment groups, respectively). Although the ADA were detected in a high proportion of subjects, most of the ADA titre values were low at 100 or 300 in both treatment groups. Moreover, all subjects who had ADA results on Day 253 (EOS) showed ADA negative results at that time point.

In both treatment groups, 100% of subjects had at least one positive ADA result after administration. However, only 2/74 (2.7%) subjects in the CT-P41 groups and 2/77 (2.6%) subjects in the US-Prolia group had at least one ADA/NAb positive result during the study. The ADA titre values at the time of NAb positive result were all low at 100. All these 4 subjects were ADA negative on Day 253 (EOS).

No TEAEs classified as drug-related hypersensitivity/allergic reactions were reported during the study for the Safety Set.

The applicant conducted post-hoc analyses from Studies CT-P41 1.2 and CT-P41 3.1 to determine if immunogenicity had impact on clinical outcomes.

The analyses for primary PK parameters ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max}) by ADA status and titre at Day 15 and Day 141 in Study CT-P41 1.2. No relationship between ADA status and PK parameters is observed.

Similarly, there was no relationship between ADA status and titre with the PD parameters S-CTX and S-P1NP.

During Study CT-P41 1.2 up to Day 253, the proportion of subjects who experienced any treatment-emergent adverse event (TEAE) and Grade 3 or higher TEAE was analysed by ADA status and titre at Day 141. There were no treatment-emergent serious AE (TESAE) and TEAE classified as drug-related hypersensitivity/allergic reaction in Study CT-P41 1.2.

There was overall no apparent correlation between the rate of immune-related AEs and ADA positivity. The proportion of subjects with at least one TEAE and TEAE over Grade 3 was lower in the ADA positive group than in the ADA negative group and the AEs were comparable between the treatment groups.

Table 12. Summary of AEs by ADA status and titre in study CT-P41 1.2: safety set

Adverse Event	CT-P41 (N=74)	US-Prolia (N=77)
Number of subjects with ≥ 1 TEAE		
ADA Negative	7/8 (87.5%)	7/8 (87.5%)
ADA Positive	47/64 (73.4%)	51/67 (76.1%)
ADA Titre = 100	31/37 (83.8%)	38/50 (76.0%)
ADA titter = 300	16/27 (59.3%)	13/17 (76.5%)
ADA titre ≥ 900	-	-
Number of subjects with ≥ 1 Grade 3 or higher TEAE		
ADA Negative	1/8 (12.5%)	0/8 (0.0%)
ADA Positive	3/64 (4.7%)	1/67 (1.5%)
ADA titter = 100	1/37 (2.7%)	1/50 (2.0%)
ADA titre = 300	2/27 (7.4%)	0/17 (0.0%)
ADA titter ≥ 900	-	-

Note: 'Negative' includes the subgroup of ADA negative at Day 141; 'Positive' includes the subgroup of ADA positive at Day 141; titre ≥ 900 includes ADA titter of 900, 2700, and 8100 of Day141. Percentages are calculated by using the number of subjects in each ADA subgroup as denominator.
Abbreviations: ADA, anti-drug antibody; N, number of subjects in each treatment group; TEAE, treatment- emergent adverse event; US, United States

2.5.3. Discussion on clinical pharmacology

All bioanalytical methods used in the MAA were fully developed and validated by PPD Laboratory Services for Celltrion, Inc. The bioanalytical methods include quantification of denosumab concentration (PK-data), determination of PD-markers (CTX-1 and P1NP) concentrations and detection of ADA and NAb against denosumab (immunogenicity) in human serum. In general, the validation of all bioanalytical methods has been performed in accordance with relevant guidelines and are considered acceptable.

For the determination of serum CTX-1 and total P1NP in human serum has been used. Specificity, selectivity and stability was taken from the respective manufacturer's package insert that has been provided. Furthermore, CoAs of all calibrator and QC lots used for CTX-1 and total P1NP analysis have been provided. The provided information is considered acceptable. Concentrations of the quality controls (QCs) used for calibration in the course of CTX-1 and P1NP measurements are not in line with concentration ranges suggested in the ICH M10 guideline. However, the concentration of the QCs has been chosen in accordance with the reference ranges that have been taken from the manufacturer's kit insert. Furthermore, the reference ranges for CTX-1 and P1NP were verified by the applicant by analysing samples collected from healthy volunteers (CTX-1: 4447 samples, total P1NP: 4450 samples). Chosen concentrations of the QCs have been sufficiently justified and are acceptable.

PK studies

The PK/PD characteristics of CT-P41 were investigated in one pilot study (i.e., study CT-P41 1.1), in one pivotal PK study (i.e., study CT-P41 1.2) and one pivotal efficacy and safety study (i.e., study CT-P41 3.1). From the PK point of view, the PK results from the pivotal study CT-P41 1.2 are the most important and the PK data from the other two studies have only a supportive role.

The study CT-P41 1.1 was a pilot phase 1, randomised, double-blind, two-arm, parallel group, single-dose (60 mg SC injection) study in healthy male subjects (n=30, 15 in each group) in which the primary objective was to evaluate safety. The PK/PD were as secondary endpoints. Mean serum

concentrations of CT-P41 (60 mg) and EU-Prolia (60 mg) were generally comparable between the 2 treatment groups. Also, the studied PK parameters (i.e., secondary endpoints $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max}, T_{max}, $T_{1/2}$, %AUCext, λz, CL/F, and Vz/F) seem comparable between CT-P41 and EU-Prolia, although the mean values in the C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were slightly higher in the EU-Prolia group than in the CT-P41 group. On the basis of the provided CoAs, the protein contents of CT-P41 batch and EU-Prolia batch were 57.2 mg/ml and 59.6 mg/ml, respectively. Consequently, the slight difference in the protein contents in the used batches may partially explain the slightly higher concentrations in the EU-Prolia group compared to the CT-P41 group. The biggest difference could be seen in the median t_{max} , which occurred at ~14 and ~ 10 days for CT-P41 and EU-Prolia treatment groups, respectively. The issue of differing times of maximal concentration are not considered an issue given the small sample size in this pilot safety study. All subjects' %AUCext were < 20%. Consequently, the sampling time period up to day 134 was long enough to characterise the whole concentration-time profile of denosumab.

The study CT-P41 1.2 was a phase 1, randomised, double-blind, two-arm, parallel group, single-dose (60 mg SC injection) study, in which the primary objective was to demonstrate PK similarity between CT-P41 and US-Prolia in healthy male subjects. PD and safety were secondary objectives. The study design was acceptable, and the study population was as advised by the CHMP. A subtherapeutic dose was scientifically preferred by the CHMP (e.g., a dose of 35 mg using Xgeva vial as the reference product). However, also the use of 60 mg dose was considered acceptable and the applicant selected the 60 mg dose (i.e., Stoboclo 60 mg/ml PFS presentation of the CT-P41 as the test product and Prolia 60 mg/ml PFS as the reference product) to this study.

Study recruitment started on 06.10.2021 and the study was completed on 20.10.2022. There was only one statistical analysis plan dated 09 March 2023, and the database lock was dated 10 March 2023.

Amendment 3 (Protocol version 1.3) was performed after study start (dated 22 July 2022) and included updated contact information of CRO and SAE reporting method, updated policies of sample storage/ shipping, clarification of statistical methods and addition of an analytical facility for PD testing. No significant changes were made to the original protocol that could interfere with study analysis as the revision for sample storage and shipment was only applicable to the back-up samples to be stored after the CT-P41 1.2 study completion.

The PK/PD and immunogenicity sampling timepoints, as well as the study duration up to 9 months, were adequate. The PK/PD data analysis and statistical methods used were justifiable. Of the 154 randomised subjects, 151 subjects were dosed (n = 74 subjects in the CT-P41 group and n = 77 subjects in the US-Prolia group) and all of these subjects were included in the PK, PD and safety analysis sets. Overall, demographics and baseline characteristics were similar between the two treatment groups (age range from 28 to 55 years, BMI 24.80 kg/m^2). Subjects were stratified according to body weight (< 80 kg vs. ≥ 80 kg) on Day -1 and study centre. Both factors were well balanced between the two treatment groups.

The protein content of the CT-P41 batch was 60.1 mg/ml on the basis of the provided CoA. For the used US-Prolia batch, no data on protein content exist. The measured protein concentrations for ten US-Prolia batches in the biosimilarity demonstration were in the range of 59.6-61.1 mg/ml. It is unlikely that the protein content of the used US-Prolia batch has been different than batches used in the biosimilarity demonstration.

The $\%AUC_{extrap}$ were < 20% for all subjects indicating that the sample time period was long enough.

The geometric LS means of the primary PK parameters (i.e., $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}) were similar between the two treatment groups. The 90% CIs for the ratio of geometric LS means were within the equivalence margin of 80% to 125% for all 3 primary endpoints, indicating the similarity between CT-

P41 and US-Prolia in terms of PK. It is noted that the lower limit of 90%CI of $AUC_{0\text{-}inf}$ was slightly over 100% and the 90%CI consequently did not include 100%. This is, however, not considered to be an issue.

Also, the means of secondary PK parameters (i.e., $T_{1/2}$, $pAUC_{0\text{-}W16}$ and $pAUC_{W16\text{-}inf}$, %AUCext, λz, CL/F, Vz/F, MRT) median T_{max} were comparable between the study treatments.

The overall PK profile of the CT-P41 treatment group was similar to the US-Prolia treatment group.

Thus, study CT-P41 1.2 demonstrated PK similarity between CT-P41 and US-Prolia in healthy male subjects.

The study CT-P41 3.1 was a phase 3, double-blind, randomised, active-controlled, parallel group study to compare efficacy, PK/PD and safety of CT-P41 and US-Prolia in postmenopausal women with osteoporosis. Patients received an initial dose of 60 mg SC injection of CT-P41 or US-Prolia on day 1 (week 0), followed by the study drug on week 26 during the treatment period I, and then at week 52 during treatment period II. The protein contents of the test and referenced product batches used in study CT-P41 3.1 were very similar.

The concentration (ng/ml) -time (weeks) profiles of denosumab were very similar between CT-P41 and US-Prolia groups both at treatment period I and treatment period II.

The mean concentrations in CT-P41 group at different study weeks from day 3 to the EOS were slightly higher than in the US-Prolia group, however, the concentrations could be considered to be comparable between study groups. The same trend could be seen in the C_{trough} concentrations at weeks 0, 26, and 52. The mean C_{trough} concentrations were slightly higher in the CT-P41 group than in the US-Prolia group.

The calculated PK parameters (i.e., C_{max}, $AUC_{0\text{-}t}$,$T_{max,}$ Vd and $T_{1/2}$) were all at similar level between studied treatments. The geometric LS mean ratios (90% CI) were 106.72 (102.40, 111.22) for C_{max} and 107.87 (102.98, 112.98) for $AUC_{0\text{-}t}$. Although the 90% CIs of both C_{max} and $AUC_{0\text{-}t}$ did not include unity hinting at a slightly higher exposure of CT-P41, these were within 80-125% and excluded clinically important differences. Results are consistent with the results of the pivotal Phase I study CT-P41 1.2.

In all clinical studies, CT-P41 60 mg/ml PFS presentation (Stoboclo 60 mg/ml PFS) was used as the test product, which corresponds to the Prolia 60 mg/ml PFS. No clinical study was conducted with the CT-P41 120 mg/1.7 ml vial presentation (Osenvelt 120 mg/1.7 ml vial), which corresponds the Xgeva 120 mg/1.7 ml vial. In the pilot study, the reference product was EU-Prolia and in other studies, the comparator product was US-Prolia. The CHMP has advised that a robust analytical comparability data package to the EU-products must be presented at the time of MAA, if the reference product in the clinical studies is sourced from US instead of being sourced from EU, which has been provided.

Consequently, the biosimilarity of PK has been demonstrated between CT-P41 using Stoboclo 60 mg/ml PFS presentation and US-Prolia 60 mg/ml PFS. The final decision of the CT-P41 biosimilarity to EU-Prolia 60 mg PFS and to EU-Xgeva 120 mg/1.7 ml depends on the analytical comparability data, which is also considered to be appropriate.

PD studies

The applicant has provided 3 studies on pharmacodynamics to compare CT-P41 and US/EU-Prolia (Study CT-P41 1.1, CT-P41 1.2, and CT-P41 3.1).

Study CT-P41 1.1 was a safety study in 32 healthy male volunteers randomised 1:1 to receive CT-P41 or EU-Prolia. The curves for median percent change from baseline for s-CTX as well as for P1NP serum

concentration following a single SC administration of CT-P41 or EU-Prolia were overlapping. Based on descriptive data, no difference between treatments after single 60 mg SC dose were present in sampling period up to Day 134.

Study CT-P41 1.2 was conducted in healthy male volunteers. The secondary PD endpoint was geometric LS mean ratio of s-CTX and procollagen type 1 N-terminal propeptide (P1NP) AUEC over the study period of 253 days. The point estimate of the LS geometric mean ratio (CT-P41 vs. US-Prolia) for AUEC was 101.35% with the 95% CI between 97.19% and 105.68%, the margin being entirely contained within the conventional equivalence limits of 80% to 125%. The corresponding figures for P1NP were 93.35% (95% CI; 83.55%, 104.29%), the outcome meeting the prespecified acceptance criteria. In another secondary endpoint, percent change from baseline of s-CTX and P1NP at each study visit, the time-concentration curves for CT-P41 and US-Prolia groups practically overlap at each visit timepoints up to D141 for the s-CTX parameter and throughout the whole 1-year treatment period for the P1NP parameter. Difference in terminal elimination phase was observed in the s-CTX1 values, with the faster turn towards baseline observed in the US-Prolia group after cessation of the drug effect. Since the terminal elimination phase is less sensitive for assessment of biosimilarity as the measurement errors and variability increases, this issue is not pursued further.

The applicant clarified that in the analyses of AUEC initially submitted in the MAA any rebound area that crossed the baseline was not included in the AUEC. Rebound values (positive numbers of % change from baseline) were converted to 0 to exclude area above the baseline from % change from baseline versus time curve. The netAUEC results where the rebound area is subtracted were provided of each study. In Study CT-P41 1.2, there were 9 subjects with rebound in s-CTX; 4 subjects in the CT-P41 group and 5 subjects in the US-licensed Prolia group. In Study CT-P41 3.1, 16 patients experienced a rebound of s-CTX over the initial 6 months period; 11 patients in the CT-P41 group and 5 patients in the US-licensed Prolia group. It is agreed that the number of participants who experienced rebound of s-CTX was very low in both studies, and the comparison of AUEC and netAUEC results showed that the impact from the rebound effect on mean or median values was insignificant.

Study CT-P41 3.1 was the Phase 3 study in women with post-menopausal osteoporosis (PMO). The PD marker AUEC of s-CTX over the initial 6 months was a co-primary endpoint. The point estimate of the ratio (CT-P41 vs. US-Prolia) of the LS geometric mean was 94.94% with the corresponding 95% CI being [90.75%; 99.32%]. Even though the 95% CI was within the acceptance range the CI did not include value 100%, being though close to it. Of note, the CI being clearly within the acceptance margin albeit 100% was not reached, and 95% CI being fully contained within the standard acceptance range of 80-125%, the retrospective analysis is not called for. Furthermore, the ANCOVA model for the primary PD endpoint was adjusted for baseline s-CTX level (as well as the stratification factors age, baseline BMD T-score at the lumbar spine, prior bisphosphonates therapy) excluding the bias caused by the study population characteristics. Therefore, the issue was not pursued further. For CT-P41 1.2 and CT-P41 3.1 studies, minimum concentration of s-CTX (I_{min})/P1NP (I_{min}), maximum percent inhibition of s-CTX (Imax)/P1NP(Imax), and time to reach I_{min} of s-CTX/P1NP (T_{min}) were similar between groups.

The secondary PD endpoint in CT-P41 3.1 was the AUEC of P1NP over the initial 6 months. The geometric LS mean ratio was 84.04 with the 95% CI between 73.23 and 96.43. i.e. the geometric LS mean AUEC of P1NP in the US-Prolia group was statistically significantly higher than that of the CT-P41 group. Contrary to this finding in PMO patients, no difference was observed in the HV study 1.2. The difference may have been driven by 4 patients in the CT-P41 group who exhibited unusually low P1NP AUECs over the initial 6 months. All results indicated that there was no impact from concurrent diseases, baseline characteristics, and PK exposures on the P1NP AUEC of these 4 patients. Therefore, no reason for the difference in outcomes or to exclude these patients was found. The GMR result under discussion could be considered to be largely a result of an artefact created by the data derivation, since

the "raw" P1NP values do not raise concern about a difference between the products. Therefore, this issue was not pursued further.

Other secondary PD endpoints in Study CT-P41 3.1 were the serum concentrations of s-CTX and P1NP in different timepoints. The curves for both PD markers between the CT-P41 and US-Prolia groups were practically overlapping at each visit timepoints throughout the whole 1-year treatment period in Treatment Period I. However, at 26-week extension period (Treatment period II) the s-CTX level seems to return faster towards the baseline level in US-Prolia groups than in the CT-P41 group.

This effect seems to be similar also in Study 1.2, where the drug effect returned to the baseline faster in the US-Prolia group at the terminal elimination phase. This observation does not seem to correlate with the LS-BMD results, in which the difference between treatments seem to remain small and similar in magnitude after treatment period I. It is acknowledged though that the drug effect on BMD is slower than what is seen in dynamic bone-turnover markers. Of note, the s-CTX bone-turnover marker correlation with the clinically important effect in fracture incidence is not confirmed and the validation data on it is not yet available. However, in the terminal elimination phase the measurement errors and variability increases, hence, the terminal elimination phase is considered not suitable for confirmatory assessment of biosimilarity. Therefore, this issue is not pursued further.

For study CT-P41 3.1, the ICEs of use of prohibited drugs and changes in concomitant medication and missing data were compared between treatment arms from Baseline to Week 26. In the FAS the number (%) of patients with at least 1 ICE was similar between the CT-P41 and US-licensed Prolia groups (14 [5.9%] and 11 [4.6%] patients, respectively). In general numbers were low, use of prohibited drugs was similar (10 [4.2%] and 9 [3.8%] patients, respectively), a small difference is seen for changes in concomitant medication (5 [2.1%] and 2 [0.8%] patients, respectively). The number (%) of patients with missing AUEC of s-CTX was 2 (0.8%) each in the 2 groups. An analysis for the primary PD endpoint using a treatment policy for intercurrent events and imputing for missing data was provided together with a tipping point analysis showing robustness of the conclusion of equivalence. The estimate of geometric LS mean ratio and its 95% confidence interval (CI) obtained using ANCOVA is 97.09% (90.93%, 103.68%). However, this was only done for the primary PD endpoint of AUEC of s-CTX and not for AUEC of P1NP over the initial 6 months. For the latter no equivalence criterion was specified. Due to the low number of missing data, this will nevertheless not be further pursued.

An analysis using a hypothetical strategy for intercurrent events and imputing for missing data was provided: The geometric LS mean ratio and its 95% CI was 97.14% (90.85, 103.85) which was fully contained within the pre-defined equivalence margin of 80% to 125%. Again, like for imputing for missing data and using a treatment policy for intercurrent events, results on AUEC of s-CTX over the initial 6 months, i.e. the 95% CI included 1.

The primary PD endpoint result was robust concerning the impact of ICEs and missing data.

Immunogenicity

To investigate immunogenicity, ADA against CT-P41 and Prolia were evaluated using a 3-tiered step approach (screening assay, confirmatory assay, and titration assay for quantification). The neutralizing capability of confirmed ADA positive samples was investigated subsequently.

Similar immunological profiles were seen for CT-P41 and EU-Prolia in study CT-P41 1.1 and for CT-P41 and US-Prolia in study CT-P41 1.2. Close to all subjects developed ADA during both studies, and the proportion of ADA positive subjects peaked at Day 57 in study CT-P41 1.1 and at Day 85 in study CT-P41 1.2. Even though ADA were detected in a high proportion of study subjects, most of the ADA titre values were low at 100 or 300 in both treatment groups in both studies.

One subject in study CT-P41 1.1 (in the CT-P41 group) and none in the EU-Prolia group had an ADA/NAb positive sample; and this subject was NAb negative again at EOS visit. In study CT-P41 1.2, four (4) subjects had positive NAb results at least once, two (2) subjects in both treatment groups. However, all study subjects, incl. these 4 subjects with NAb, had turned ADA (and NAb) negative when tested on Day 253 (EOS). The ADA titre values at the time of NAb positive result were all low at 100. A significantly higher incidence of ADAs has been reported compared to the ADA incidence reported in the studies for MAA of Prolia. However, the ADA incidence between the CT-P41 and US/EU-Prolia arms is comparable.

The observed incidence of a positive antibody test result may be influenced by several factors, including assay methodology and sample properties. Consequently, comparison of antibodies to denosumab in the development program of CT-P41 vs. studies conducted for other products may be misleading. Post hoc analyses from Study CT-P41 1.2 showed no impact of ADA status on PK, PD, or safety. Hence, no concern is raised on the high incidence of ADA in the clinical studies of CT-P41. No TEAEs classified as drug-related hypersensitivity/allergic reactions were reported in studies CT-P41 1.1 and CT-P41 1.2. There were no apparent effects caused by ADA on PK, PD or safety.

2.5.4. Conclusions on clinical pharmacology

The biosimilarity of PK has been demonstrated between CT-P41 using Stoboclo 60 mg/ml PFS presentation and US-Prolia 60 mg/ml PFS. Nonetheless, the final decision of the CT-P41 biosimilarity to EU-Prolia 60 mg PFS and to EU-Xgeva 120 mg/1.7 ml depends on the analytical comparability data, which is considered to be appropriate.

The PD equivalence criteria was met in Phase PK/PD study (CT-P41 1.2), and the 95% confidence interval went within the range also in the co-primary PD endpoint. In the CT-P41 3.1. study, the unity was not met, but 95% CI for the geometric LS mean ratio went clearly within acceptance range of 80% - 125%. Overall, the pharmacological results support the PK and PD similarity of the denosumab biosimilar CT-P41 and reference product US-Prolia. Differences in the secondary PD endpoint P1NP were observed between the CT-P41 group and the US-licensed Prolia group in the PMO patient, while no difference was observed in the HV study CT-P41 1.2. Nevertheless, this issue was not pursued further.

2.5.5. Clinical efficacy

2.5.5.1. Dose response study(ies)

No dose response studies were performed. This is acceptable as they are not deemed necessary in the biosimilarity setting.

2.5.5.2. Main study(ies)

Study CT-P41 3.1

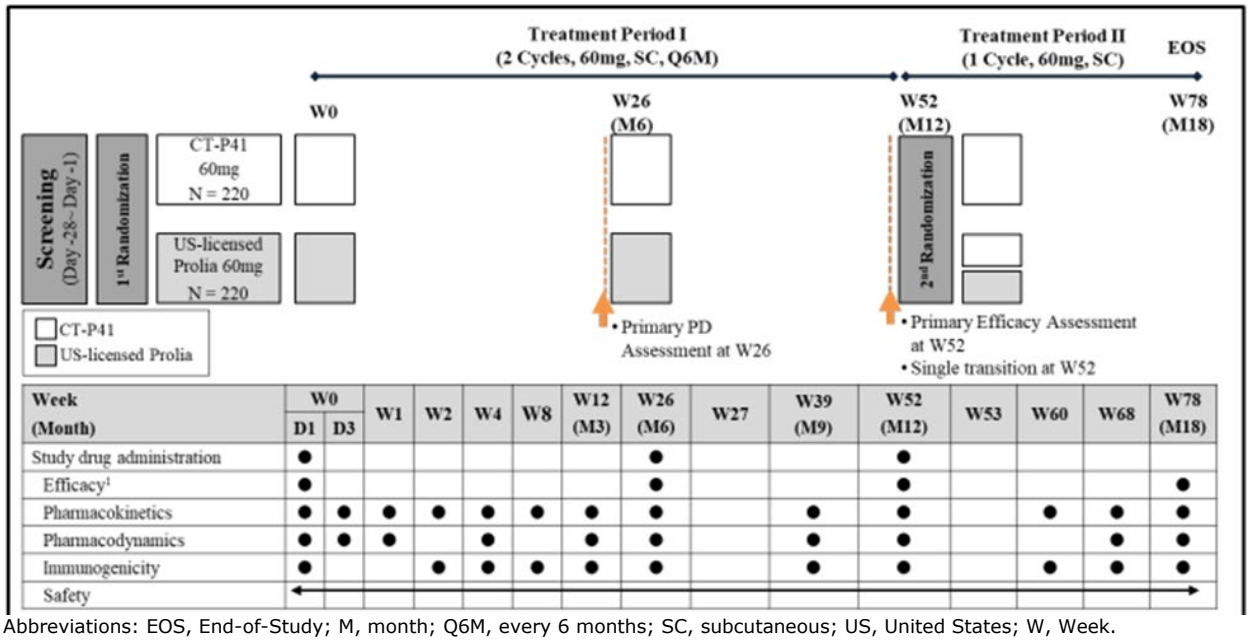
Methods

Study CT-P41 3.1 is a randomised, double-blind, active-controlled, parallel group, Phase 3 study to compare the efficacy, PK, PD, immunogenicity and overall safety of CT-P41 and US-Prolia in postmenopausal women with osteoporosis. The study comprised a 4-week screening period, a 52-week treatment period I and a 26-week treatment period II. For the patients who completed the Study CT-P41 3.1, the total duration of the treatment period was 82 weeks.

A total of 479 PMO patients were randomly assigned on Day 1 (first randomisation) 1:1 to receive two 60 mg s.c. doses of CT-P41 or US-Prolia with 6-month period in between doses. At Week 52 (second randomisation) half of the patients in US-Prolia group were re-randomised in blind to switch to receive CT-P41 and half of the control group subjects continued with their initially allocated treatment. All patients in the CT-P41 group continued to treatment period II. CT-P41 and US-Prolia were given by healthcare professionals using pre-filled syringe (PFS). All patients will also receive daily supplementation containing at least 1,000 mg of elemental calcium and at least 400 IU vitamin D.

Bone mineral density was to be assessed by DXA at Screening and at Weeks 26, 52, and 78 (EOS visit). Assessment of lumbar spine, total hip, and femoral neck BMD were performed at a central imaging vendor. At Week 52, the DXA scan was analysed by both the central imaging vendor and the study centre. The local reading results at Week 52 were used for the stratification factor of the second randomisation.

The Phase 3 study design is presented in Figure 14 below.



Week (Month)	W0 D1	W0 D3	W1	W2	W4	W8	W12 (M3)	W26 (M6)	W27	W39 (M9)	W52 (M12)	W53	W60	W68	W78 (M18)
Study drug administration	●							●			●				
Efficacy[1]	●							●			●				●
Pharmacokinetics	●	●	●	●	●	●	●	●		●	●		●	●	●
Pharmacodynamics	●	●	●		●		●	●		●	●			●	●
Immunogenicity	●			●	●	●	●	●		●	●		●	●	●
Safety	←														→

Abbreviations: EOS, End-of-Study; M, month; Q6M, every 6 months; SC, subcutaneous; US, United States; W, Week.

Figure 14. Study design overview

- **Study Participants**

Inclusion criteria

1. Women aged 50 to 80 years, both inclusive.

2. Body weight ≥40.0 and ≤99.9 kg

3. Postmenopausal women diagnosed with osteoporosis. Postmenopausal status was defined by at least 12 consecutive months of amenorrhea prior to the date of screening with FSH level ≥30 mIU/mL assessed by central laboratory at Screening visit, or surgical menopause (bilateral oophorectomy with or without hysterectomy) ≥12 months prior to the Screening visit.

4. Bone mineral density T-score ≤− 2.5 and ≥− 4.0 at the lumbar spine (L1 to L4) as assessed by the central imaging vendor based on DXA scan at Screening.

5. Patient had at least 3 vertebrae considered evaluable at the lumbar spine (L1 to L4) and at least 1 hip considered evaluable by DXA scan assessed by the central imaging vendor at Screening. Patient with unilateral metal in hips that could be allowed for the other side of 1 evaluable hip was included.

6. Patient and/or their legally authorised representative was informed and given ample time and opportunity to read and/or understand the nature and purpose of this study including possible risks, side effects and requirements for supplementation, and had signed the ICF before any study specific procedures.

Exclusion criteria

1. Patient who had previously received denosumab (Prolia, Xgeva, or biosimilar denosumab), any other monoclonal antibodies (e.g., romosozumab), or biologic agents for osteoporosis.

2. Patient with a hypersensitivity to any component of denosumab or dry natural rubber (a derivative of latex).

3. Patient who was confirmed or suspected with infection of Coronavirus disease 2019 (COVID-19) at Screening or had contact with COVID-19 patient within 14 days from Screening.

4. Patient who had a concurrent or history of any of the following infections:

a) A known infection with active hepatitis B, hepatitis C, or HIV. A patient with past hepatitis B virus was allowed if resolved.

b) Any severe or active infection or history of any infection requiring hospitalisation, parenteral antibiotics within 4 weeks prior to the first administration of the study drug, or oral antibiotics within 2 weeks prior to the first administration of the study drug

5. Patient who had a medical history of and/or current disease including any of the following(s):

a) One severe or >2 moderate vertebral fractures (severe fracture is defined as >40% vertebral height loss and moderate fracture was defined as 25% to 40% vertebral height loss as determined by central reading of lateral spine X-ray

b) Hip fracture

c) Hyperparathyroidism or hypoparathyroidism, irrespective of current controlled or uncontrolled status

d) Current hyperthyroidism (unless well controlled on stable antithyroid therapy) or current hypothyroidism (unless well controlled on stable thyroid replacement therapy)

e) Bone disease and metabolic disease (except for osteoporosis) that might interfere with the interpretation of the results

f) History of severe skeletal pain with bisphosphonates

g) History and/or current oral or dental conditions including osteomyelitis or ONJ; active dental or jaw condition which requires oral surgery; planned invasive dental procedure (e.g., tooth extraction, dental implants, oral surgery); unhealed dental oral surgery

h) History of any malignancy within 5 years prior to the first administration of the study drug except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ. Any history of bone metastases, implant radiation involving the skeleton, or skeletal malignancies were exclusionary

i) New York Heart Association (NYHA) Class III or IV chronic heart failure, any unstable cardiovascular disease, pulmonary disease, autoimmune disease, or ECG abnormalities which could be judged as clinically significant at the investigator’s discretion

6. Patient had one of the following laboratory test results at Screening:

a) Serum 25-OH vitamin D <20 ng/mL (if vitamin D deficiency was supplemented at the investigator's discretion, and retest result showed the level above 20 ng/mL within the Screening period, the patient could be enrolled in the study. The retest was limited up to twice within the Screening period)

b) Estimated glomerular filtration rate <30 mL/min/1.73 m2

c) Haemoglobin <10 g/dL

7. Patient who had a history of and/or concurrent use of medications including any of the following:

a) Receipt of intravenous bisphosphonates, fluoride, and strontium for osteoporosis within the last 5 years prior to the first administration of the study drug

b) Receipt of oral bisphosphonates ⩾3 years cumulatively prior to Screening or receipt of any dose of oral bisphosphonates within 12 months prior to Screening

c) Use of parathyroid hormone (PTH) or its derivatives, systemic hormone-replacement therapy (oestrogen with or without progestogen), selective oestrogen-receptor modulator, tibolone, calcitonin, or calcitriol within 12 months prior to the first administration of the study drug

d) Use of other bone active drugs including heparin, anticonvulsants (except benzodiazepines), systemic ketoconazole, anabolic steroids, testosterone, androgens, adrenocorticotropic hormone, cinacalcet, aluminium, lithium, protease inhibitors, methotrexate, or gonadotropin-releasing hormone agonists within 3 months prior to the first administration of the study drug

e) Use of oral or parenteral glucocorticosteroids (>5 mg/prednisone daily or equivalent for >10 days) within 3 months prior to the first administration of the study drug

f) Receipt of any investigational drug within 4 weeks or five half-lives (whichever was longer) prior to the first administration of the study drug

g) Receipt of any authorised COVID-19 vaccines within 2 weeks prior and after the first administration of the study drug (total of 4 weeks)

8. Patient who had a current alcohol or drugs abuse or a history of alcohol or drug abuse within 12 months prior to the first administration of the study drug.

9. Patient who had evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicated the use of an investigational product (IP) or could have interfere with the interpretation of study results, or patient was at high risk for treatment complication in the opinion of the investigator.

- **Treatments**

During the Treatment Period I, patients received 60 mg of either CT-P41 or US-licensed Prolia on Week 0 (Day 1) and Week 26, as per the first randomisation. During the Treatment Period II, patients received 60 mg of either CT-P41 or US-licensed Prolia at Week 52 as per the second randomisation. The study drug was administered as a single SC injection in the upper arm, upper thigh, or abdomen.

All patients were to also receive daily supplementation containing at least 1,000 mg of elemental calcium and at least 400 IU vitamin D from randomisation to End-of-Study (EOS) visit, and the data are collected via patient's diary.

If a patient developed hypercalcaemia during the study, the calcium and/or vitamin D supplementation was to be discontinued or reduced at the investigator's discretion until the serum calcium concentration returned to the normal range.

If a patient developed hypocalcaemia, including albumin-adjusted total serum calcium <8.5 mg/dL (<2.125 mmol/L) during the study, appropriate additional supplementation was to be instituted as deemed acceptable by local guidelines to return the serum calcium concentration within the normal range.

If a patient was intolerant to the daily calcium or vitamin D supplementation, the formulation was changed, or the dose was lowered at the investigator's discretion. The intolerance, as well as the resolution (e.g., change in formulation or dosage), was to be recorded in both the source documents and the eCRF.

Patients who were discontinued from the study drug or were terminated from the study could be transitioned to another anti-resorptive therapies at the investigator's discretion.

- **Objectives**

Primary objectives:

- To demonstrate the equivalence of CT-P41 to US-licensed Prolia in terms of efficacy in postmenopausal women with osteoporosis as determined by percent change from baseline in bone mineral density (BMD) for lumbar spine (L1 to L4) at Week 52
- To demonstrate the pharmacodynamics (PD) similarity in terms of area under the effect curve (AUEC) of serum carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) over the initial 6 months (from Day 1 predose to Week 26 predose) between CT-P41 and US-licensed Prolia

Secondary objectives

The secondary objectives were to evaluate additional efficacy, PK, PD, and overall safety including immunogenicity of CT-P41 compared with US-Prolia.

- **Outcomes/endpoints**

Co-Primary endpoints

The primary efficacy endpoint was the following:

- Percent change from baseline in BMD for lumbar spine (L1 to L4) by dual-energy X-ray absorptiometry (DXA) at Week 52

The primary PD endpoint was the following:

- Area under the effect curve of s-CTX over the initial 6 months (from Day 1 predose to Week 26 predose)

Secondary efficacy endpoints

- Percent change from baseline in BMD for lumbar spine (L1 to L4), total hip, and femoral neck by DXA at Weeks 26, 52, and 78
- The incidences of new vertebral, nonvertebral, and hip fractures during the study
- Change from baseline in health-related quality of life at Weeks 26, 52, and 78

Secondary pharmacokinetic endpoints

The secondary PK endpoints assessed over the first 26 weeks were the following:

- Maximum serum concentration (C_{max}) after the first administration of study drug (over the initial 6 months [26 weeks])
- Truncated area under the concentration-time curve from zero to Week 26 (AUC_{0-t})
- Time of observed maximum serum concentration (T_{max}) of denosumab after the first administration of the study drug
- Volume of distribution (Vd)
- Terminal elimination half-life (T1/2)

The secondary PK endpoints assessed up to Week 78 were the following:

- Serum concentration of denosumab
- Trough serum concentration (C_{trough}) (concentration prior to the next study drug administration)

Secondary pharmacodynamic Endpoints

- Area under the effect curve (AUEC) of procollagen type 1 N-terminal propeptide (P1NP) over the initial 6 months (from Day 1 predose to Week 26 predose)
- Percent change from baseline of s-CTX and P1NP at Weeks 26, 52, and 78

- **Sample size**

A sample size of 352 patients (176 patients per group at Week 52) was supposed to achieve 90% statistical power for the demonstration of similarity of percent change from baseline in BMD for lumbar spine at Week 52, based on the two one-sided 2.5% significance level and an equivalence margin of ± 1.503%. Common SD of 3.89% and mean difference of zero were assumed. The dropout rate was hypothesised as 20%; therefore, approximately 440 patients (220 patients in each treatment group of CT-P41 and US-Prolia) were to be randomised.

For the demonstration of the PD similarity between CT-P41 and US-Prolia by ratio of geometric means of AUEC of s-CTX over the initial 6 months, a sample size of 396 patients (198 patients per group) was supposed to achieve at least 90% statistical power based on the two one-sided 2.5% significance level and an equivalence margin of 80% - 125%. In this sample size calculation, the CV of 50 % and mean ratio of 1 were assumed. Accounting for 10% of drop-out rate, 440 patients (220 patients per group) were to be randomised to achieve the required sample size of 198 patients per group.

Consequently, 440 patients were to be randomised to evaluate efficacy and PD similarities.

Of note: the originally planned (Protocol Version 1.0) sample size was 416 patients to be randomised but this was revised to 440 in Protocol Version 2.0 (08 April 2021), i.e., before the first patient was randomised.

- **Randomisation and Blinding (masking)**

On Day 1, patients were randomly assigned in a 1:1 ratio to receive 60 mg of either CT-P41 or US-Prolia. The randomisation was stratified by age (<65 vs. ≥65 years), baseline BMD T-score at the lumbar spine (≤− 3.0 vs. >− 3.0) and prior bisphosphonates therapy (Yes vs. No).

Prior to dosing at Week 52, patients in the US-Prolia group were randomly assigned again in a ratio of 1:1 to either undergo transition to CT-P41 (switching arm) or continue US-Prolia (non-switching arm). The second randomisation was stratified by change from baseline in BMD for lumbar spine at Week 52 (≥3% versus <3%). All patients who were initially randomly assigned to CT-P41 on Day 1 (Week 0)

continued their treatment with CT-P41 on Week 52. Still, the second randomisation process was conducted in all groups to maintain the study blind.

An interactive web response system (IWRS) was used for the randomisation. Unblinded biostatisticians generated the randomisation schedule, balanced by using permuted blocks, for IWRS.

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. Patients were blinded through the use of a blindfold, screen or similar method during the dosing procedure so that the injection syringe was not visible to patient. Blinded staff was absent during injection and remained blinded throughout the study.

- **Statistical methods**

The co-primary endpoints were evaluated in the Full Analysis Set (all patients that received at least 1 full dose of study drug) using all available data regardless of study drug discontinuation, protocol violation, or receipt of alternative therapy. The primary efficacy analysis for percent change in LS-BMD was repeated in the Per Protocol set: those who received all 2 doses (full) of study drug (CT-P41 or US-Prolia) at Weeks 0 (Day 1) and 26 and had LS-BMD assessments at baseline and Week 52 and encountered no major protocol deviation that might affect the interpretation of study results of primary efficacy endpoint. Notably, for patients who discontinued study drug early or initiated different osteoporosis medication (including those prohibited by the protocol), scheduled assessments were to be completed only until the next study drug administration.

The analysis of the percent change from baseline in LS-BMD at Week 52 was conducted using an analysis of covariance (ANCOVA) model considering the treatment as a fixed effect and age, baseline BMD T-score at the lumbar spine, and prior bisphosphonates therapy (Yes versus No) as covariates. Missing data imputation was not considered for the primary efficacy analysis. Therapeutic equivalence of clinical efficacy was to be concluded if the 95% CI for the treatment difference between the CT-P41 group and US-Prolia group was entirely within equivalence margin of −1.503% to +1.503%.

The impact of missing data on primary efficacy results was evaluated under missing at random (MAR) scenario as well as missing not at random (MNAR) scenario.

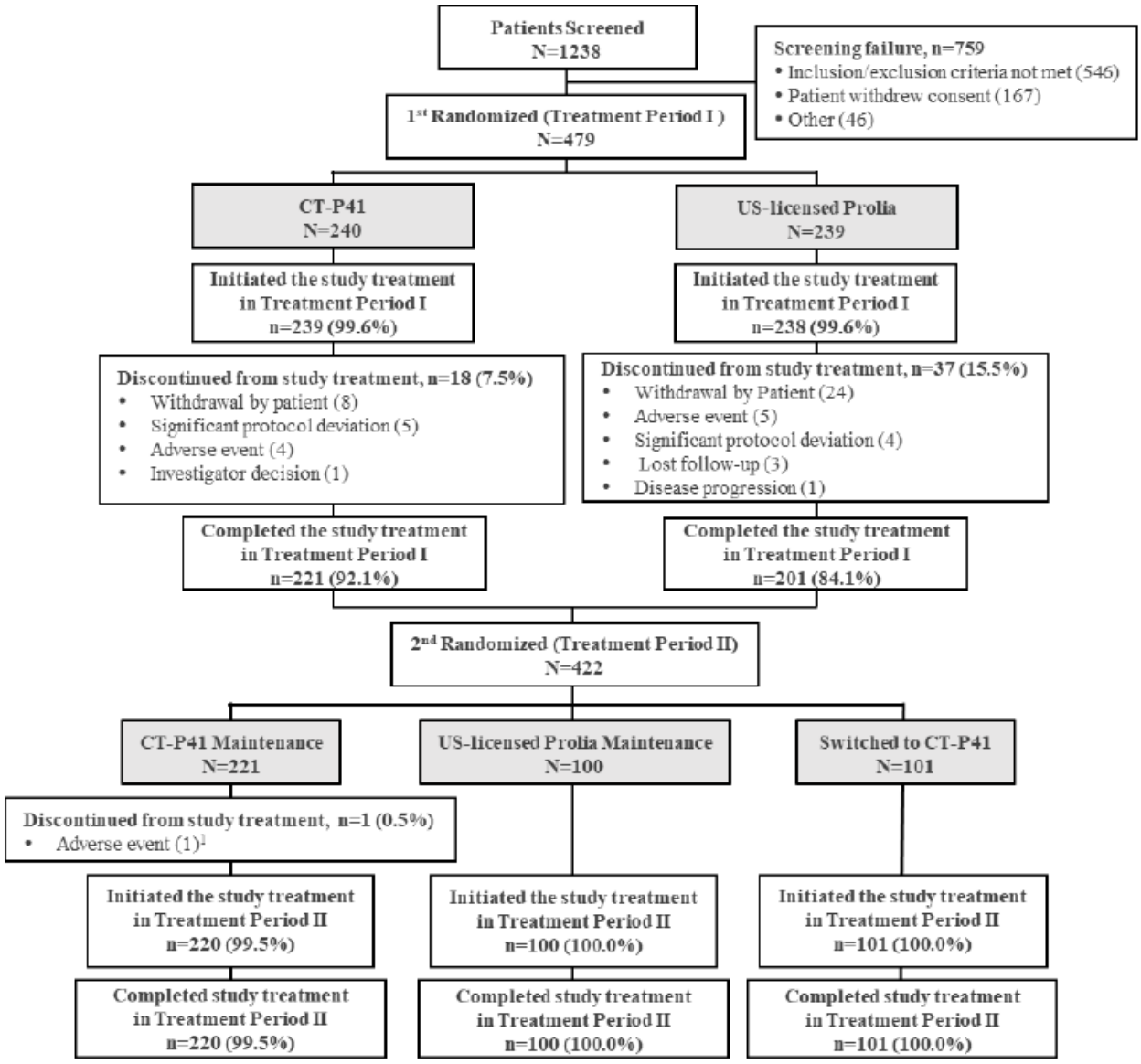
Sensitivity analyses were conducted. Firstly, missing percent change from baseline in BMD values for lumbar spine at Week 52 was imputed by the average of non-missing percent change from baseline in LS-BMD values at Week 52 in each treatment group (mean imputation), suggested by the applicant to represent missing at random assumption. Secondly, in a tipping point analysis, the imputed cases by the above method were shifted upwards gradually in each group until the 95% CI was no longer entirely within the therapeutic equivalence margin of ±1.503%.

The analysis of the log-transformed AUEC of s-CTX over the initial 6 months was conducted using an ANCOVA model including the treatment as a fixed effect and age, baseline BMD T-score at the lumbar spine, prior bisphosphonates therapy (Yes versus No) and baseline s-CTX level as covariates. Back transformation of LS means difference (CP-P41 and US-Prolia) provided the ratio of geometric means and 95% CI for the ratio. Statistical equivalence was to be declared if the 95% CI for the ratio of the geometric LS mean between CT-P41 and US-Prolia fell entirely within an equivalence margin of 80% to 125%. For patients who did not have serum concentration result of s-CTX/P1NP at Week 26, AUEC of s-CTX were excluded.

Results

- **Participant flow**

Figure 15. Participant flow. Summary of patient disposition (treatment period I and II): ITT set and ITT-treatment period II subset



1. One patient in the CT-P41 maintenance group was randomly assigned to receive the study drug at Week 52 visit but the study treatment was discontinued due to the ongoing adverse event. The patient continued the study participation without the study treatment and completed Treatment Period II.

- **Recruitment**

Study initiation date was 17 June 2021 (first patient randomised) and the date of data cutoff on 18 May 2023 (the last patient's Week 52 visit). No formal interim analyses were performed. After the database lock for the first CSR data (all data for patients who signed the ICF between May and August 2021 and data up to Week 52 for patients who signed the ICF in April 2022), the study was unblinded for the reporting purposes. With D120 responses for this procedure, the final CSR data were provided.

Completion date of study CT-P41 3.1 was 16 November 2023 (last patient's last visit). Date of the final clinical study report was 12 March 2024. The final CSR included data of all patients who completed the study (up to Week 78, end-of study [EOS]) or terminated their study participation early.

The study initially aimed to conduct 100% source data verification (SDV) of all data, from the screening visit to all completed visits by reviewing source document on-site by site monitors. However, due to potential on-site visit restriction of COVID-19 pandemic, the applicant implemented a targeted SDV instead, ensuring 100% verification of the critical dataduring on-site interim monitoring visit.

- **Conduct of the study**

Amendments

Protocol identification: CT-P41 3.1; EudraCT no. 2020-005974-91; date of final protocol (v00, original protocol): 28-Sep-2018

The study protocol was amended seven times.

Amendment 1 including country specific protocol, dated 23 December 2020

- Updated the efficacy, PK, and PD endpoints as discussed with FDA
- Revised the efficacy, PK, and PD analysis as per the FDA's comment
- Specified missing data imputation for primary efficacy endpoint as per the FDA's comment
- Revised subgroups analysis to be conducted by race and age instead of geographic regions as per the FDA's comment
- Revised the study design as only efficacy was set as primary endpoint per the discussion with FDA Revised the PD assessments as only efficacy was set as primary endpoint per the discussion with FDA Revised the sample size calculation as the statistical power and equivalence margin were changed and efficacy was set as primary endpoint
- Revised the discontinuation of study drug details as only efficacy was set as primary endpoint per the discussion with FDA

Amendment 2 including country specific protocol, dated 04 January 2021

- Added the plan for statistical test for secondary efficacy endpoints
- Supplemented the definition of major deviation

Amendment 3 including country specific protocol, dated 30 April 2021

- Added the explanation for co-primary endpoints as per the comment of MFDS

Amendment 4 (global), dated 08 April 2021

- Updated inclusion criteria to specify assessment timepoint for DXA scan and updated exclusion criteria to specify osteoporosis treatment and the criteria for ONJ
- Revised the study design to clarify the EOS visit procedure for patients who discontinued study drug early
- Revised secondary efficacy endpoints assessment to analyse the incidences of new vertebral fracture, nonvertebral fracture and hip fracture
- Updated safety assessment details by adding the atypical femoral fracture as an AESI, description for ONJ, and oral examination to be included in the physical examination
- Updated the statistical assumption by correcting the CI from 90% to 95% as per the comment of EMA and revised the study sample size to 440 from 416.
- Revised the analysis set for primary efficacy endpoint, secondary efficacy endpoints and primary PD endpoint as per the comment of EMA.

- Added a definition of FAS-Treatment Period II Subset according to the revised efficacy analysis set
- Added the rationale for historical data selection as per the comment of EMA
- Added the description to make patients, who were discontinued from the study drug or were terminated from the study, transitioned to another anti-resorptive therapy upon conclusion of study drug therapy as per the comment of FDA
- Added caution for people who sensitive to latex
- Revised incidences of fractures details to collect information of fractures not limited to new clinical fracture; revised vertebral fractures details to collect information of vertebral fracture regardless of the presence of patient-reported symptoms indicative of a fracture; revised nonvertebral fractures details to exclude pathologic fractures and collect information of fractures not limited to new clinical fracture
- Added the information of PK, PD, and immunogenicity sampling for patients who early discontinue study drug
- Updated the AESI assessment including atypical femoral fracture, ONJ, and drug-related hypersensitivity/allergic reaction
- Added the information of injection site reaction, hypersensitivity/allergic reaction monitoring, and local site pain assessments for patients who early discontinue study drug
- Added text to assess the NYHA for patients who have history of heart failure
- Added the clinical laboratory tests of low-density lipoprotein, thyroid stimulating hormone, and intact parathyroid hormone for safety assessment

Amendment 5 including country specific protocol, dated 21 May 2021

- Applied changes implemented in global protocol amendment Version 2.0 to the country-specific protocol amendment B.1, Version 1.0.
- Added smoking history collection to medical history, disease history, and demographic information

Amendment 6 (global), dated 30 July 2021

- Updated the number of study centres and countries
- Updated exclusion criteria to clarify the drugs for osteoporosis and systemic hormone-replacement therapy, to include other bone active drugs and to restrict the COVID-19 vaccination
- Updated replacement and rescreening of patients to allow patients not to repeat specific assessments who have eligible results within 28 days before the first administration of the study drug
- Modified prohibited therapies by adding the systemic hormone-replacement therapy which was missed in the previous version and added specific therapy to clarify and adding any authorised COVID-19 vaccines
- Added the analysis of listing of patients whose trial participation is impacted by COVID-19 to reflect the contents of FDA guidance for the conduct of clinical trials of medical products during the COVID-19 public health emergency

Amendment 7 including country specific protocol, dated 18 April 2022

- Applied changes implemented in global protocol amendment Version 2.0 and Version 2.1 to the country-specific protocol amendment A.0, Version 1.0.
- Considering the Ukraine issue, updated the SAP for the primary efficacy endpoint and sensitivity analysis of primary efficacy endpoint as per FDA’s response

- Added the description that the lateral spine X-ray at Week 26 or Week 52 can be performed at a separate site visit within the visit window
- Added smoking history collection to medical history, disease history, and demographic information
- Added the description for the final determination of the major protocol deviations to analysis set

Protocol compliance

Table 13. Major protocol deviations and other reasons for exclusion from the analysis set (treatment period I): ITT set and significant GCP non-compliance patients

Treatment Period I	CT-P41 (N=240)	US-licensed Prolia (N=239)	Total (N=479)	Excluded from Following Sets
	Number (%) of patients			
Number (%) of patients with at least one major protocol deviation	5 (2.1%)	5 (2.1%)	10 (2.1%)	
Major protocol deviation				
Receiving any prohibited medication which affect primary result	3 (1.3%)	5 (2.1%)	8 (1.7%)	PPS
Non-adherence to inclusion or exclusion criteria which affect primary result	2 (0.8%)	0	2 (0.4%)	PPS
Other reasons for exclusion				
No BMD assessments for lumbar spine (L1 to L4) at baseline or Week 52	18 (7.5%)	27 (11.3%)	45 (9.4%)	PPS
The full dose was not administered at Week 0 or Week 26	15 (6.3%)	25 (10.5%)	40 (8.4%)	PPS
No post-treatment PK concentration data prior to dosing at Week 52	3 (1.3%)	3 (1.3%)	6 (1.3%)	PK set
No post-treatment PD concentration data prior to dosing at Week 52	3 (1.3%)	3 (1.3%)	6 (1.3%)	PD set
The full dose was not administered at all	1 (0.4%)	1 (0.4%)	2 (0.4%)	FAS, PK set
The dose was not administered at all	1 (0.4%)	1 (0.4%)	2 (0.4%)	Safety set
The full dose was not administered at Week 0	1 (0.4%)	1 (0.4%)	2 (0.4%)	PD set

Abbreviations: BMD, bond mass density; FAS, Full analysis set; GCP, good clinical practice; ITT, intent-to-treat; PD, pharmacodynamic; PK, pharmacokinetic; PPS, Per-protocol set; US, United States.

Table 14. Major protocol deviations and other reasons for exclusion from the analysis set (treatment period II): ITT-treatment period II subset and significant GCP non-compliance patients

Treatment Period II	CT-P41 Maintenance (N=221)	US-licensed Prolia Maintenance (N=100)	Switched to CT-P41 (N=101)	Total (N=422)	Excluded from Following Sets
	Number (%) of patients				
Number (%) of patients with at least one major protocol deviation	0	0	0	0	
Other reasons for exclusion					
No post-treatment PD concentration data after Week 52	5 (2.3%)	3 (3.0%)	1 (1.0%)	9 (2.1%)	PD subset
No post-treatment PK concentration data after Week 52	3 (1.4%)	3 (3.0%)	1 (1.0%)	7 (1.7%)	PK subset
The full dose was not administered at Week 52	1 (0.5%)	0	0	1 (0.2%)	FAS subset, PK subset, PD subset
The dose was not administered as Week 52	1 (0.5%)	0	0	1 (0.2%)	Safety subset

Abbreviations: FAS, Full analysis set; GCP, good clinical practice; ITT, intent-to-treat; PD, pharmacodynamic; PK, pharmacokinetic; US, United States.
Sources: Post-text Table 14.1.3.

In Treatment Period I, 104 (43.3%) patients of the CT-P41 group reported at least 1 visit that occurred OOW and 34 (14.2%) patients reported at least 1 missing visit. Furthermore, 212 (9.0%) visits occurred OOW, and 60 (2.5%) visits were missed. In comparison, 116 (48.5%) patients of the US-licenced Prolia group reported at least 1 visit that occurred OOW and 46 (19.2%) patients reported at least 1 missing visit. Furthermore, 222 (9.5%) visits occurred OOW, and 71 (3.0%) missing visits. The average period of visits that occurred OOW was 8.7 days for the CT-P41 group and 8.3 days for the US-licensed Prolia group.

In Treatment Period II, 90 (40.7%) patients of the CT-P41 Maintenance group reported at least 1 visit that occurred OOW, and 7 (3.2%) patients reported at least 1 missing visit. 159 (14.5%) visits occurred OOW, and 9 (0.8%) visits were missed. Of the US-licensed Prolia Maintenance group 43 (43.0%) patients reported at least 1 visit that occurred OOW, and 6 (6.0%) patients reported at least 1 missing visit. Furthermore, 69 (13.8%) visits occurred OOW, and 12 (2.4%) visits were missed. In the Switched to CT-P41 group 47 (46.5%) patients reported at least 1 visit that occurred OOW, and 6 (5.9%) patients reported at least 1 missing visit. Moreover, 77 (15.3%) visits occurred OOW, and 7 (1.4%) visits were missed. The average period of visits that occurred OOW was 7.0, 11.3, and 8.2 days in the CT-P41 Maintenance group, US-licensed Prolia Maintenance group, and Switched to CT-P41 group, respectively.

During the overall study period, 52/328 patients, whose visits were OOW or missed, discontinued the study treatment. Reasons for discontinuation was "withdrawal by patient" (29 patients), "adverse event" (10 patients), „lost to follow up" or „significant protocol deviation" (12 patients) and „disease progression" (1 patient). Furthermore, 54/328 patients, whose visits were either OOW or missed, terminated the study participation early. Reasons for study termination were "withdrawal by patient" (32 patients), "left the city or country" or were not possible to follow up due to the war in Ukraine (12

patients), "lost to follow-up" (3 patients), "adverse event", "personal" or "death" (2 patients each), and "overly exceeded visit window" (more than 2 months; 1 patient).

Cases of patients who discontinued the study drug or terminated the study participation early which was possibly affected by the violated visits were distributed as follows:

In Treatment Period I, 5 patients of the CT-P41 group and 7 patients of the US-licenced Prolia group discontinued study drug and terminated the study participation early. Reasons in the US-licenced Prolia group were "lost to follow up" (3 patients) or "due to war, subject is out of Ukraine" (4 patients). Reasons in the CT-P41 group were "due to war, subject leave the country and couldn't complete study visits" (3 patients), "due to war, subject is out of Ukraine" or "missed third IP dose due to the war" (1 patient each).

For Treatment Period II, 2 patients of the CT-P41 Maintenance group and one patient of the US-licensed Prolia Maintenance group terminated the study early. Reasons for early termination were "subject moved to another city" or "subject moved to another country".

Table 15. Number of Ukraine patients and visits affected by war: ITT set

Ukraine Site Number	3401	3402	3403	3404	Total
Number of patients randomized	18	31	9	20	78
Number of patients affected by war in Ukraine	11	14	1	13	39
Number of visits affected by war in Ukraine	31	34	4	34	103

Abbreviation: ITT, intent-to-treat.

- **Baseline data**

The demographic characteristics at baseline in ITT population for Treatment Period I is described in Table 16 below.

Table 16. Demographic characteristics at baseline, ITT population – TP1

Parameter Statistic/Characteristic	CT-P41 (N=240)	US-licensed Prolia (N=239)	Total (N=479)
Age (years)			
n	240	239	479
Mean (SD)	65.5 (6.26)	65.9 (6.58)	65.7 (6.42)
Median	66.0	66.0	66.0
Min, Max	50, 79	51, 79	50, 79
Ethnicity, n (%)			
Hispanic or Latino	0	3 (1.3)	3 (0.6)
Non-Hispanic or Non-Latino	240 (100.0)	236 (98.7)	476 (99.4)
Race, n (%)			
White	240 (100.0)	239 (100.0)	479 (100.0)
Height (cm)			
n	240	239	479
Mean (SD)	160.51 (6.003)	159.44 (5.967)	159.98 (6.003)
Median	160.25	159.20	160.00
Min, Max	140.0, 173.5	143.0, 178.0	140.0, 178.0
Weight (kg)			
n	240	239	479
Mean (SD)	64.14 (10.894)	64.06 (10.906)	64.10 (10.889)
Median	63.00	64.00	63.00
Min, Max	43.0, 99.4	40.2, 99.9	40.2, 99.9
Body mass index (kg/m^2)			
n	240	239	479
Mean (SD)	24.92 (4.230)	25.23 (4.328)	25.08 (4.277)
Median	24.35	24.80	24.60
Min, Max	15.9, 40.6	16.5, 41.4	15.9, 41.4
Age group, n (%)			
<65 years	101 (42.1)	101 (42.3)	202 (42.2)
≥65 years	139 (57.9)	138 (57.7)	277 (57.8)
Baseline BMD T-score at lumbar spine, n (%)			
≤-3.0	120 (50.0)	120 (50.2)	240 (50.1)
>-3.0	120 (50.0)	119 (49.8)	239 (49.9)
Prior bisphosphonates therapy, n (%)			
Yes	32 (13.3)	28 (11.7)	60 (12.5)
No	208 (86.7)	211 (88.3)	419 (87.5)

Abbreviations: BMD, bone mineral density; ITT, intent-to-treat; Max, maximum; Min, minimum; SD, standard deviation; US, United States.

Table 17. Demographics and stratification details at week 52: ITT-treatment period II subset

Parameter Statistic/Characteristic	**CT-P41 Maintenance (N=221)**	**US-licensed Prolia Maintenance (N=100)**	**Switched to CT-P41 (N=101)**	**Total (N=422)**
Demographic Characteristics				
Age (years)				
n	221	100	101	422
Mean (SD)	65.4 (6.23)	65.5 (6.65)	66.1 (6.47)	65.6 (6.38)
Median	66.0	66.5	66.0	66.0
Min, Max	50, 79	51, 79	54, 79	50, 79
Ethnicity, n (%)				
Hispanic or Latino	0	0	2 (2.0%)	2 (0.5%)

Parameter Statistic/Characteristic	**CT-P41 Maintenance (N=221)**	**US-licensed Prolia Maintenance (N=100)**	**Switched to CT-P41 (N=101)**	**Total (N=422)**
Non-Hispanic or Non-Latino	221 (100.0)	100 (100.0)	99 (98.0)	420 (99.5)
Race, n (%)				
White	221 (100.0)	100 (100.0)	101 (100.0)	422 (100.0)
Height (cm)				
n	221	100	101	422
Mean (SD)	160.58 (5.897)	158.57 (5.896)	160.55 (5.845)	160.10 (5.929)
Median	160.50	159.00	160.00	160.00
Min, Max	145.0, 173.5	143.0, 178.0	144.0, 175.0	143.0, 178.0
Weight (kg)				
n	221	100	101	422
Mean (SD)	64.53 (11.013)	63.64 (11.547)	64.67 (9.609)	64.35 (10.809)
Median	63.00	62.15	64.00	63.40
Min, Max	43.0, 99.4	40.2, 99.9	47.4, 93.0	40.2, 99.9
Body mass index (kg/m^2)				
n	221	100	101	422
Mean (SD)	25.05 (4.255)	25.37 (4.849)	25.10 (3.531)	25.14 (4.239)
Median	24.40	24.45	25.00	24.60
Min, Max	16.3, 40.6	16.5, 38.2	17.0, 33.0	16.3, 40.6
Stratification Factor at Week 52				
Percent change from baseline in BMD for lumbar spine at Week 52, n (%)				
<3%	62 (28.1)	27 (27.0)	26 (25.7)	115 (27.3)
⩾3%	159 (71.9)	73 (73.0)	75 (74.3)	307 (72.7)

Abbreviations: ITT, intent-to-treat; Max, maximum; Min, minimum; SD, standard deviation; US, United States.

The baseline disease characteristics in ITT set are summarised in Table 18 below.

Table 18. Baseline disease characteristics: ITT set

	CT-P41 (N=240)	US-licensed Prolia (N=239)	Total (N=479)
	Number (%) of Patients		
Vertebral fracture			
Number of patients with at least 1 vertebral fracture at baseline	59 (24.6%)	50 (20.9%)	109 (22.8%)
Nonvertebral fracture			
Number of patients with at least 1 nonvertebral fracture	75 (31.3%)	93 (38.9%)	168 (35.1%)
BMD T-score at baseline			
Lumbar spine			
n	239	238	477
Mean (SD)	-3.073 (0.3966)	-3.077 (0.3766)	-3.075 (0.3864)
Median	-3.010	-2.990	-3.010
Min, Max	-4.00, -2.51	-3.97, -2.51	-4.00, -2.51
Total hip			
n	239	238	477
Mean (SD)	-1.701 (0.6616)	-1.691 (0.7010)	-1.696 (0.6809)
Median	-1.710	-1.695	-1.710
Min, Max	-3.60, 0.10	-3.49, 0.53	-3.60, 0.53
Femoral neck			
n	239	238	477
Mean (SD)	-1.988 (0.6126)	-1.974 (0.6037)	-1.981 (0.6076)
Median	-2.010	-2.015	-2.010
Min, Max	-3.99, -0.05	-3.31, -0.25	-3.99, -0.05
Years since menopause			
n	240	239	479
Mean (SD)	16.7 (7.46)	16.6 (7.56)	16.7 (7.50)
Median	16.0	16.0	16.0
Min, Max	2, 39	2, 38	2, 39
Smoking history			
Current smoker	46 (19.2%)	40 (16.7%)	86 (18.0%)
Former smoker	30 (12.5%)	36 (15.1%)	66 (13.8%)
Never smoker	164 (68.3%)	163 (68.2%)	327 (68.3%)

Abbreviations: BMD, bone mineral density; ITT, intent-to-treat; Max, maximum; Min, minimum; SD, standard deviation; US, United States.

The prior and concurrent medical history data was provided for both groups; it was highly comparable by the data available from different SOC groups. Osteopenia was reported in 3 (1.3%) patients in each group, which is interesting since in all study subjects the loss of bone density should have progressed to the level of osteoporosis. Of the disease groups that might have an impact on progression of osteoporosis also in a group of disease in SOC group "renal and urinary disorders", the number of patients suffering of these was adequately comparable being 27 (11.3%) in CT-P41 group and 38 (15.9%) in US-Prolia group. The number of patients in SOC group "Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)" was 54 (22.5%) in CT-P41 group and 65 (27.2%) in US-Prolia group. The number of patients in SOC group "Metabolism And Nutrition Disorders" was 102 (42.5%) for CT-P41 and 107 (44.8%) for US-Prolia group. The SOC groups with the most frequently reported medical histories were musculoskeletal and connective tissue disorders, which was reported in 279 (58.2%) and vascular disorders reported in 243 (50.7%) patients.

Altogether, 319 (66.9%) patients (160 [66.9%] patients in the CT-P41 group and 159 [66.8%] patients in the US-licensed Prolia group) had taken at least 1 prior medication. No significant difference

between treatment groups were observed in patients having used osteoporosis predisposing medication. Of the drugs in a drug class "Drugs For Treatment Of Bone Diseases", IV BP had used 14 (5.8%) patients in the CT-P41 group and 8 (3.4%) in US-Prolia group, oral BP 22 (9.2%) patients in CT-P41 group and 18 (7.5%), not specified BP treatment 2 patients in each group, and strontium 3 (1.3%) patients in CT-P41 group

- **Numbers analysed**

The analysis sets in Treatment Period I and treatment Period II are summarised in Table 19 and Table 20 below.

Table 19. Analysis sets (treatment period I): ITT set

Analysis Set	CT-P41 (N=240)	US-licensed Prolia (N=239)	Total (N=479)
	Number (%) of Patients		
Intent-to-Treat (ITT) Set	240 (100.0%)	239 (100.0%)	479 (100.0%)
Full Analysis Set (FAS)	239 (99.6%)	238 (99.6%)	477 (99.6%)
Per-Protocol Set (PPS)	215 (89.6%)	202 (84.5%)	417 (87.1%)
Pharmacokinetic (PK) Set	237	236	473
Pharmacodynamic (PD) Set	237	236	473
Safety Set	239	238	477

Abbreviations: FAS, full analysis set; ITT, intent-to-treat; PD, Pharmacodynamic; PK, pharmacokinetic; PPS, Per-protocol Set; US, United States.
Note: For ITT Set, FAS and PPS, counts were from randomized treatment and percentages were calculated using the ITT Set as a denominator. For PK Set, PD Set and Safety Set, counts were from actual treatment received.

Table 20. Analysis sets (treatment period II): ITT-treatment period II subset

Analysis Subset	CT-P41 Maintenance (N=221)	US-licensed Prolia Maintenance (N=100)	Switched to CT-P41 (N=101)	Total (N=422)
	Number (%) of Patients			
ITT-Treatment Period II Subset	221 (100.0%)	100 (100.0%)	101 (100.0%)	422 (100.0%)
FAS-Treatment Period II Subset	220 (99.5%)	100 (100.0%)	101 (100.0%)	421 (99.8%)
PK-Treatment Period II Subset	218	97	100	415
PD-Treatment Period II Subset	216	97	100	413
Safety-Treatment Period II Subset	220	100	101	421

Abbreviations: FAS, full analysis set; ITT, intent-to-treat; PD, Pharmacodynamic; PK, pharmacokinetic; US, United States.
Note: For ITT-Treatment Period II Subset and FAS-Treatment Period II Subset, counts were from randomized treatment and percentages were calculated using the ITT-Treatment Period II Subset as a denominator. For PK-Treatment Period II Subset, PD–Treatment Period II Subset and Safety-Treatment Period II Subset, counts were from actual treatment received.
Source: Post-text Table 14.1.1.

- **Outcomes and estimation**

Primary efficacy analysis

Co-primary endpoints of the study were the percent change from baseline (%cfb) in BMD for lumbar spine (L1 to L4) by DXA at Week 52 (efficacy) and %cfb in the AUEC of s-CTX (PD). The results for the PD co-primary endpoint are assessed in Section 3.3.1.2 of this AR.

The primary efficacy endpoint, %cfb in BMD for lumbar spine (L1 to L4) by DXA at Week 52 is assessed here. The outcome data is summarised for the FAS and PPS in the table below.

Table 21. Percent change from baseline in BMD for lumbar spine by DXA at week 52 (ANCOVA): FAS and PPS (complete case analysis)

Analysis set Group	n/N	LS Mean (SE)	LS Mean Difference	95% CI of LS Mean Difference
FAS				
CT-P41	222/239[1]	4.9317 (0.31508)	-0.139	(-0.826, 0.548)
US-licensed Prolia	212/238[1]	5.0706 (0.32714)		
PPS				
CT-P41	215/215[2]	5.0330 (0.31640)	-0.280	(-0.973, 0.414)
US-licensed Prolia	202/202[2]	5.3125 (0.33505)		

Abbreviations: ANCOVA, analysis of covariate; BMD, bone mineral density; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; FAS, full analysis set; LS, least squares; PPS, Per-protocol Set; SE, standar error; US, United States.

Note: An ANCOVA was performed with the treatment as a fixed effect and age, baseline BMD T-score at the lumbar spine, and prior bisphosphonates therapy (yes versus no) as covariates.

1. The number of patients who had a BMD assessment result for lumbar spine by DXA at Week 52 / The number of patients in FAS.
2. The number of patients who had a BMD assessment result for lumbar spine by DXA at Week 52 / The number of patients in PPS.

Sensitivity Analysis by Tipping Point Analysis:

The sensitivity analysis by a tipping point analysis for the primary efficacy endpoint was conducted. The impact of missing data on the primary efficacy results was evaluated under MAR scenario, then a tipping point analysis was performed to evaluate the impact of missing data under MNAR scenario.

The number of patients with missing value in percent change from baseline in BMD of lumbar spine at Week 52 for the CT-P41 and US-Prolia groups was 43 patients (17 [7.1%] and 26 [10.9%] patients, respectively). Based on the information provided by the applicant, to reach the tipping points that change the conclusion of equivalence, the missing values of the CT-P41 group would need to be shifted by around 13% while there was no shift in the US-licensed Prolia group. Also missing values of the US-Prolia group would need to be shifted by around 7% while there was no shift in the CT-P41 group.

The primary efficacy endpoint was examined post hoc in subgroups defined by the stratification factors (age, baseline BMD T-score at lumbar spine and prior bisphosphonate therapy) and a number of additional factors (country, BMI at Screening, baseline BMD T-score at total hip, baseline BMD T-score at femoral neck and presence of vertebral fracture at baseline). For datasets restricted to members of each subgroup, an ANCOVA similar to the primary analysis was fitted (excluding the fixed effect defining the subgroup).

There were no significant discrepancies in the percent change from baseline in BMD for lumbar spine at Week 52 between the subgroups.

Secondary endpoints:

Percent change from baseline in BMD for lumbar spine (L1 to L4), total hip, and femoral neck by DXA at Weeks 26, 52, and 78.

Actual value and percent change from baseline in BMD for lumbar spine, total hip, and femoral neck by DXA for Treatment Period I (FAS) and Treatment Period II (FAS-Treatment Period II Subset) are summarised in Table 22 and Table 23.

Table 22. Descriptive statistics for actual result and percent change from baseline in BMD for lumbar spine, total hip, and femoral neck (treatment period I): FAS

Anatomical Site / Visit / Statistic	CT-P41 (N=239)		US-licensed Prolia (N=238)	
	Actual Result	Percent Change from Baseline	Actual Result	Percent Change from Baseline
Lumbar spine				
Baseline				
n	239		238	
Mean	0.7454		0.7446	
SD	0.06787		0.06457	
Min	0.612		0.610	
Median	0.7400		0.7420	
Max	0.879		0.878	
Week 26				
n	225	225	219	219
Mean	0.7730	3.7945	0.7714	3.4845
SD	0.07057	3.41660	0.06914	3.46721
Min	0.615	-4.942	0.605	-5.416
Median	0.7720	3.9627	0.7660	3.2832
Max	0.938	12.784	0.956	14.088
Week 52				
n	222	222	212	212
Mean	0.7854	5.4913	0.7866	5.6621
SD	0.07157	3.79907	0.06816	3.75768
Min	0.596	-5.806	0.619	-5.336
Median	0.7805	5.4557	0.7860	5.5910
Max	0.963	17.623	0.952	17.869
Total hip				
Baseline				
n	239		238	
Mean	0.7558		0.7570	
SD	0.08606		0.09369	
Min	0.503		0.516	
Median	0.7550		0.7500	
Max	1.021		1.051	
Week 26				
n	222	222	218	218
Mean	0.7710	1.7879	0.7651	1.2857
SD	0.08793	2.55484	0.09289	2.78147
Min	0.495	-7.343	0.504	-6.566
Median	0.7685	1.8694	0.7570	1.2834
Max	1.043	11.044	1.019	12.117
Week 52				
n	219	219	212	212
Mean	0.7789	2.7914	0.7717	2.4253
SD	0.08765	2.87044	0.09264	2.84061
Min	0.501	-6.108	0.519	-8.621
Median	0.7790	2.9372	0.7700	2.6031
Max	1.040	12.353	1.009	12.396
Femoral neck				
Baseline				
n	239		238	
Mean	0.6702		0.6723	
SD	0.10217		0.10963	
Min	0.379		0.461	
Median	0.6620		0.6585	
Max	0.959		0.993	
Week 26				
n	222	222	218	218
Mean	0.6819	1.5721	0.6802	1.2337
SD	0.10629	3.57808	0.11200	3.67343
Min	0.417	-14.354	0.454	-11.057
Median	0.6780	1.5391	0.6745	1.3365
Max	0.980	13.712	1.023	11.774
Week 52				
n	219	219	212	212
Mean	0.6869	2.2295	0.6846	1.9476
SD	0.10390	4.02031	0.11155	3.86739
Min	0.425	-10.196	0.465	-9.201
Median	0.6820	2.2792	0.6725	2.0200
Max	0.994	14.917	1.021	16.170

Abbreviations: BMD, bone mineral density; FAS, full analysis set; Max, maximum; Min, minimum; SD, standard deviation; US, United States.

Table 23. descriptive statistics for actual result and percent change from baseline in BMD for lumbar spine, total hip, and femoral neck (treatment period II): FAS-treatment period II subset

Anatomical Site / Visit / Statistics	CT-P41 Maintenance (N=220)		US-licensed Prolia Maintenance (N=100)		Switched to CT-P41 (N=101)	
	Actual Result	Percent Change from Baseline	Actual Result	Percent Change from Baseline	Actual Result	Percent Change from Baseline
Lumbar spine						
Week 78						
n	213	213	97	97	98	98
Mean	0.7953	6.8588	0.7923	6.5745	0.8010	7.0532
SD	0.07520	4.12795	0.06463	3.40437	0.06790	3.55985
Min	0.612	-8.412	0.651	-2.814	0.660	-0.565
Median	0.7890	6.7204	0.7890	6.9602	0.7985	7.1262
Max	0.980	20.765	0.951	15.097	0.951	16.713
Total hip						
Week 78						
n	213	213	96	96	98	98
Mean	0.7830	3.4706	0.7683	2.7947	0.7914	3.3837
SD	0.08829	2.81017	0.09102	2.79862	0.09486	2.92786
Min	0.527	-5.599	0.546	-5.918	0.565	-3.177
Median	0.7800	3.4370	0.7650	3.0629	0.7795	3.4139
Max	1.039	14.469	0.961	8.883	1.018	11.838
Femoral neck						
Week 78						
n	213	213	96	96	98	98
Mean	0.6910	2.9995	0.6871	2.4429	0.6996	2.8226
SD	0.10453	3.73072	0.11420	3.61786	0.10689	4.02021
Min	0.459	-10.049	0.461	-9.970	0.469	-6.140
Median	0.6870	2.8701	0.6755	3.2504	0.6905	2.9085
Max	0.980	17.365	1.024	8.115	1.042	15.840

Abbreviations: BMD, bone mineral density; FAS, full analysis set; Max, maximum; Min, minimum; SD, standard deviation; US, United States.
Source: Post-text Table 14.2.4.1.

The incidence of new vertebral, nonvertebral, and hip fractures for Treatment Period I (FAS), Treatment Period II (FAS-Treatment Period II Subset), and overall period (FAS) are summarised in Table 24 and Table 25.

Table 24. Incidence of new vertebral, nonvertebral, and hip fractures (treatment period I): FAS

Type of Fracture / Site of Fracture	CT-P41 (N=239)	US-licensed Prolia (N=238)
New vertebral fracture	**1 (0.4%)**	**1 (0.4%)**
T8	0	1 (0.4%)
L2	1 (0.4%)	0
Nonvertebral fracture[1]	**2 (0.8%)**	**4 (1.7%)**
Carpus, Right	1 (0.4%)	0
Fibula Distal, Left	0	1 (0.4%)
Humerus Proximal, Left	0	1 (0.4%)
Radius Distal, Left	1 (0.4%)	2 (0.8%)
Radius Distal, Right	1 (0.4%)	0
Hip fracture[2]	**0**	**0**

Abbreviations: FAS, full analysis set; L, lumbar vertebrae; T, thoracic vertebrae; US, United States.
Note: At each level of summarization, a patient was counted once if the patient reported one or more fractures.
1. Nonvertebral fractures of the efficacy assessment were summarized.
2. Among the nonvertebral fractures as secondary efficacy endpoint, the fractures occurring at the site of 'Femur Neck', 'Femur Intertrochanter', or 'Femur Subtrochanter' were considered as hip fracture.

Table 25. Incidence of new vertebral, nonvertebral, and hip fractures (treatment period II): FAS-treatment period II subset

Type of Fracture Site of Fracture	CT-P41 Maintenance (N=220)	US-licensed Prolia Maintenance (N=100)	Switched to CT-P41 (N=101)
New vertebral fracture	**1 (0.5%)**	**0**	**0**
L1	1 (0.5%)	0	0
Nonvertebral fracture[1]	**2 (0.9%)**	**0**	**1 (1.0%)**
Radius Distal, Right	2 (0.9%)	0	0
Ribs, Right	0	0	1 (1.0%)
Ulna Distal, Right	1 (0.5%)	0	0
Hip fracture[2]	**0**	**0**	**0**

Abbreviations: FAS, full analysis set; US, United States.
Note: At each level of summarization, a patient was counted once if the patient reported one or more fractures.
1. Nonvertebral fractures of the efficacy assessment were summarized.
2. Among the nonvertebral fractures as secondary efficacy endpoint, the fractures occurring at the site of 'Femur Neck', 'Femur Intertrochanter', or 'Femur Subtrochanter' were considered as hip fracture.
Source: Post-text Table 14.2.5.2.

Furthermore, as a secondary endpoint, the change from Baseline in Health-related Quality of Life at Weeks 26, 52, and 78 and EQ-5D-5L at Week 26 and 52 was studied.

The change from baseline for the mean value at Week 26, 52, and 78 was 0.0134, -0.3431, and 0.0820 in CT-P41 group, and respectively, 1.0534, -0.0117, and -0.1096in US-Prolia group. In emotional status, the change from baseline for the mean value at Week 26, 52, and 78 was -0.4386, -0.9867, and -1.9541in CT-P41 group, and respectively, -0.7680, -1.3154, and -3.0303 in US-Prolia group. In back pain parameter, the mean value for change from baseline at Week 26, 52, and 78 was 3.357, 3.611, and 4.147 in CT-P41 group and 2.882, 4.127, and 1.563, respectively, in US-Prolia group.

The mean EQ-5D-5L index value at Week 26,52 and 78 was 0.8222 (0.0121 change to baseline), 0.7994 (-0.0132) and 0.8045 (-0.0111) for the CT-P41 group and 0.8359 (0.0231 change from baseline), 0.8100 (-0.0057) and 0.8021 (-0.0114), respectively, for the US-Prolia group. The EQ VAS values at the same timepoints were 77.5 (change from baseline 0), 76.9 (-0.8), and 79.1 (1.4) for the CT-P41 group and 77.5 (change from baseline -0.1), 78 (0.3), and 76.5 (-1.7) for the US-Prolia.

Overall, all the changes and differences between groups in the Health-related Quality of Life parameters were minimal and have no significance on overall clinical interpretation on treatment influence.

- **Ancillary analyses**

None

- **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 biosimilarity assessment (see later sections).

Table 26. Summary of efficacy for trial CT-P41 3.1

Title: A Double-blind, Randomised, Active-controlled, Phase 3 Study to Compare Efficacy, Pharmacokinetics, Pharmacodynamics, and Safety of CT-P41 and US-licensed Prolia in Postmenopausal Women with Osteoporosis			
Study identifier	Project code: CT-P41 EudraCT number: 2020-005974-91		
Design	Randomised, active-controlled, double-blind, multicentre study		
	Duration of main phase:		Screening Period: Day –28 to Day –1 Treatment Period: Week 0 to Week 78 • Treatment Period I (52 weeks) • Treatment Period II (26 weeks) End-of-Study visit: Week 78
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	To demonstrate that CT-P41 is equivalent to US-Prolia		
Treatments groups	CT-P41		Patients received CT-P41 60 mg administered subcutaneously using PFS at Weeks 0 and 26. Number of randomised = 240
	US-Prolia		Patients received US-Prolia 60 mg administered subcutaneously using PFS at Weeks 0 and 26. Number of randomised = 239
Endpoints and definitions	Primary efficacy endpoint	Percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52	The percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52.
	Secondary efficacy endpoints	Percent change from baseline in BMD for lumbar spine (L1 to L4), total hip, and femoral neck by DXA	The percent change from baseline in BMD for lumbar spine (L1 to L4), total hip, and femoral neck by DXA at Weeks 26, 52, and 78.
		Incidences of new vertebral, nonvertebral, and hip fractures	The incidences of new vertebral, nonvertebral, and hip fractures during the study.
		Change from baseline in health-related quality of life	The change from baseline in health-related quality of life using osteoporosis assessment questionnaire short version (OPAQ-SV) and EuroQoL-5 Dimensions-5 Levels health survey (EQ-5D-5L) at Weeks 26, 52, and 78.

Database lock	31 July 2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS): The FAS was defined as all patients who received at least 1 full dose of study drug (CT-P41 or US-Prolia). The primary efficacy endpoint was the percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52.		
Descriptive statistics and estimate variability	Treatment group	CT-P41	US-Prolia
	Number of patients*	222/239	212/238
	LS mean (Standard error)	4.9317 (0.31508)	5.0706 (0.32714)
	Estimate of treatment difference (95% CI of LS mean difference)	-0.139 (-0.826, 0.548)	
	* The number of patients who had a BMD assessment result for lumbar spine by DXA at Week 52 / The number of patients in FAS.		
Analysis description	**Primary Analysis**		
Analysis population and time point description	Per-protocol set (PPS): The PPS was defined as all patients who received all 2 doses (full) of study drug (CT-P41 or US-Prolia) at Day 1 (Week 0) and Week 26; and had BMD assessments from lumbar spine at baseline and Week 52. Patients with major protocol deviation that could have affected the interpretation of study results of primary efficacy endpoint were excluded from the PPS. Final determination of the PPS was made at the blinded data review meeting (DRM) before unblinding. The primary efficacy endpoint was the percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52.		
Descriptive statistics and estimate variability	Treatment group	CT-P41	US-Prolia
	Number of patients**	215/215	202/202
	LS mean (Standard error)	5.0330 (0.31640)	5.3125 (0.33505)
	Estimate of treatment difference (95% CI of LS mean difference)	-0.280 (-0.973, 0.414)	
	** The number of patients who had a BMD assessment result for lumbar spine by DXA at Week 52 / The number of patients in PPS.		

Note: ANCOVA is performed with the treatment as a fixed effect and age, baseline BMD T-score at the lumbar spine and prior bisphosphonates therapy (yes versus no) as covariates.
Abbreviations: ANCOVA, analysis of covariance; BMD, bone mineral density; CI, confidence interval; DXA, dual energy X-ray absorptiometry; LS, least squares; PFS, prefilled syringe

2.5.5.3. Clinical studies in special populations

Not applicable for biosimilars.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Phase 3 study CT-P41 3.1 is a randomised, double-blind, active-controlled, parallel group study to evaluate the efficacy, PK, PD, immunogenicity and overall safety of CT-P41 (N=220) versus US-Prolia (N=220) in postmenopausal women with osteoporosis. A total of 1238 patients were screened and 479 patients from 20 study centres in 4 European countries (Estonia (53, 32/21), Latvia (9, 4/5), Poland (337, 164/173), Ukraine (78, 39/39) in the FAS) were enrolled in this study.

The study comprises a 4-week screening period, a 52-week treatment period I and a 26-week treatment period II. The total study duration is up to 82 weeks including 4-week screening period. The efficacy, PK/PD, safety and immunogenicity data up to Week 78 for patients who signed the informed consent form between May and August 2021 and data up to Week 52 for the patients who signed informed consent form in April 2022 are presented. The completed data from Study 3.1 was provided in the D120 answers by the applicant. The data does not change the initial interpretation of the study outcome.

The dosing of denosumab and concomitant calcium and vitamin D supplements followed the recommendations addresses in the Prolia product information. Calcium and vitamin D supplementation could be increased or reduced by investigator's discretion. The descriptive statistics for the average daily dose of calcium and vitamin D in treatment periods I and II for the safety set were similar between treatment groups.

The study design complied with the received CHMP scientific advises (EMEA/H/SA/4399/1/2020/III, EMEA/H/SA/4399/1/FU/1/2020/II, EMA/SA/0000050271). The applicant has used only US-Prolia reference in clinical studies, which is acceptable, since analytical similarity of CT-P41 has been demonstrated in a 3-way analytical similarity assessment using EU-authorised as well as US-licensed Prolia and Xgeva. Therefore, the results obtained in studies with US-Prolia as comparator can be extrapolated to EU-Prolia and Xgeva. The only differences are the presentation of the drug product, different strength of the products and minor differences in drug product formulation.

A total of 479 PMO patients were randomly assigned on Day 1 (first randomisation) to equal groups 1:1 to receive two 60 mg s.c. doses of CT-P41 or US-Prolia with 6-month period between the doses. At Week 52 (second randomisation) half of the patients in US-Prolia group were re-randomised in blind to switch to receive CT-P41 and half of the control group subjects continued with their initially allocated treatment. All patients in the CT-P41 group continued to treatment period II. The subjects received in total three s.c. doses of CT-P41 or US-Prolia. The patients were stratified by age (<65 years versus ≥65 years), baseline BMD T-score at the lumbar spine (≤-3.0 versus >-3.0) and prior bisphosphonates therapy (yes versus no). The proposed stratification factors are acceptable.

The target population, postmenopausal women with osteoporosis, is homogeneous and sensitive population to detect differences between compared treatments. Overall, the inclusion and exclusion criteria were appropriate and demographic as well as disease history characteristics was balanced between groups in TPI. However, current smokers were allowed to participate to the study. The negative dose- and age-dependent effect of smoking on bone mineral density has been reported in scientific literature. In a large meta-analysis by Ward KD et Klesges RC (Calcif Tissue Int. 2001; 68(5): 259–270) the authors reported the smokers having significantly reduced bone mass compared with nonsmokers (never and former smokers) at all bone sites, averaging a one-tenth standard deviation (SD) deficit for combined sites. Deficits were especially pronounced at the hip, where the bone mass of current smokers was one-third of a SD less than that of never smokers. This was more pronounced in elderly and current smokers. Longitudinal studies show smokers to have accelerated bone loss compared to non-smokers (Trevisan C et al. J Clin Densitom. 2020;23(3):381-389; Emaus N et al. J

Bone Miner Res. 2014;29(9):2080-2089). Thus, the inclusion of current smokers to the study brought heterogeneity to the population particularly since dose-related and cumulative effect was seen in the published report (Ward KD and Klesges RC, 2001). In addition, study sensitivity will putatively decrease since the treatment effect is expected to be worse in current smokers conveying the study outcome towards equivalence by including subjects with worse prognosis for improvement. It has been demonstrated that nicotine inhibits mineralised nodule formation by osteoblasts, and the culture medium from osteoblasts containing nicotine and lipopolysaccharide increases osteoclast differentiation (Tanaka H et al. PLoS One. 2013; 8(3): e59402). As smokers are approximately evenly distributed between groups, this issue is not pursued further.

The presented medical history between groups was overall balanced. Patients with cumulative use of oral bisphosphonates (BP) for ≥3 years and of IV BP within 5 years prior to the study were excluded; and if oral BPs were used for less than 3 years, the withdrawal period was required to have been at least 1 year from the last dose administered. It is however noteworthy that the 5-year washout period might be too short to remove BP effect on bone metabolism. This was also addressed in the received scientific advice. However, as BPs are recommended and widely used as primary treatment of osteoporosis, excluding these patients might have hampered recruitment of a sufficient number of patients in the study. Therefore, inclusion of prior users of BPs is deemed acceptable with these restrictions, and since the patients were stratified by prior BP use (both oral and IV BPs). The number of subjects with prior BP use was relatively small, and the study subjects were stratified by their prior BP use with 23 patients in the CT-P41 groups and 28 patients in the US-Prolia group having had prior BP treatment. The applicant has performed subgroup analysis on these patients and the data does not show significant difference on its impact on %cfb in LS-BMD between groups. However, stratification and subgroup analyses did not take the amount of and exact time-point of prior bisphosphonates therapy and their administration form into account. As this limitation cannot be addressed, it will remain an uncertainty, but due to randomisation a similar impact of prior BP use is likely. The exclusion criterion "patient who had previously received denosumab (Prolia, Xgeva, or biosimilar denosumab), any other monoclonal antibodies (e.g., romosozumab), or biologic agents for osteoporosis" does not limit the use in other indications (e.g. oncology indication of denosumab) potentially interfering the study outcome. Nevertheless, based on the data provided any biologicals (e.g. denosumab, romosozumab, blosozumab, teriparatide) used in osteoporosis were not present in the patients' medical history. Also, demographic and stratification details at Week 52 have been presented for Treatment Period II. Provided characteristics are balanced between treatment groups and show an even distribution of patients between treatment groups. A tabular summary of baseline disease characteristics was not presented for the treatment period II, but since this is only supplementary data for the EU-MAA issue this is not pursued further.

The co-primary objectives and endpoints of the CT-P41 3.1 study, to demonstrate the equivalence of CT-P41 to US-licensed Prolia in terms of efficacy in postmenopausal women with osteoporosis as determined by percent change from baseline in bone mineral density (BMD) for lumbar spine (L1 to L4) at Week 52 and in terms of AUEC of s-CTX over the initial 6 months between CT-P41 and US-licensed Prolia, were according to the CHMP scientific advice (EMEA/H/SA/4399/1/2020/III) and are acceptable. Even though the biomarker s-CTX is not validated to correlate with the clinically important outcome, fracture risk, it is more sensitive than the other clinically relevant LS-BMD selected as co-primary. The bone-turnover biomarker s-CTX is a dynamic marker of bone resorption with large effect size in comparison to the LS-BMD with slower and more narrow response to treatment requiring at least one year study to reach adequate sensitivity to detect differences between products. These endpoints complement each other and increase totality of evidence for the similarity in efficacy.

For BMD measurement in the lumbar spine, the measurement point (i.e., which vertebrae) was specified in the protocol (L1 to L4) and remained consistent for baseline and follow-up measurements

and the measurement was performed on validated instruments, dual-energy X-ray absorptiometry (DXA), to reduce variability. Vertebrae that were affected by local structural change or artifact were excluded, using at least 2 vertebrae for diagnostic classification. Anatomically abnormal vertebrae could be excluded from analysis if they were clearly abnormal and nonassessable within the resolution of the system. The applicant presented the number of excluded vertebrae from lumbar spine (L1 to L4) bone mineral density (BMD) assessment. More vertebrae needed to be excluded for US-licensed Prolia than for CT-P41. L4 Vertebrae needed to be excluded from BMD measurements considerably more often than L1-L3 vertebrae.

If a patient experienced fracture on the hip that had been scanned during the study up to the time of fracture, no further scans were obtained for the affected location. Even in case of fracture, the fractured location was not excluded from the lumbar spine BMD assessment unless it was structurally changed or had an artefact. For only 1 patient in the CT-P41 group the fracture location (L2) was excluded from all BMD assessments (at screening and Weeks 26, 52, and 78) due to the degenerative change at Week 26 by the central imaging vendor.

Bone mineral density changes for individual patients were to be monitored by the central imaging vendor during the study. Assessment of lumbar spine, total hip, and femoral neck BMD was to be performed at a central imaging vendor. A BMD assessor for the local reading was assigned to each study centre. All DXA scans of lumbar spine, total hip, and femoral neck BMD were to be submitted to and analysed by the central imaging vendor. At Week 52 visit, the DXA scan was analysed by both the central imaging vendor and the study centre. A strong linear correlation between reading results is observed.

The lateral spine X-ray were to be performed at Screening, Weeks 26, 52, and 78 (EOS visit), and also could be performed as required for confirmation of suspected vertebral fractures. The vertebral fracture was assessed by semi-quantitative grading at a central imaging vendor: Grade 0-3 dependent on the reduction in vertebral height.

The secondary objectives to evaluate additional efficacy, PK, PD, and overall safety including immunogenicity of CT-P41 compared with US-Prolia were approvable as well. The secondary efficacy endpoints were percent change from baseline in lumbar spine, total hip, and femoral neck BMD by DXA at Weeks 26, 52, and 78, the incidences of new vertebral, nonvertebral, and hip fractures, as well as QoL endpoints. The secondary PD endpoints were "area under the effect curve (AUEC) of procollagen type 1 N-terminal propeptide (P1NP) over the initial 6 months (from Day 1 predose to Week 26 predose) and percent change from baseline of s-CTX and P1NP at Weeks 26, 52, and 78. These are considered relevant and sufficient to support further the PD similarity between CT-P41 and US-Prolia.

For the co-primary endpoint %cfb in LS-BMD, the provided CHMP advice required preservation of at least 70% of the treatment effect and the margin considerably below 2%, which could be acceptable (EMEA/H/SA/4399/1/2020/III). The equivalence margin of ±1.503% for the %cfb in LS-BMD at Week 52 endpoint is statistically justified and acceptable as discussed in the CHMP scientific advice (EMA/SA/0000050271). However, clinical justification was not provided by the applicant in the submitted dossier. Nevertheless, as the outcome of the clinical efficacy comparison between CT-P41 and US-Prolia groups resulted in very narrow 95% confidence interval, this issue is not pursued further. The acceptability range 80%−125% for the 95% confidence interval criterion to demonstrate clinical similarity for the co-primary PD biomarker s-CTX is acceptable and was approved in the provided CHMP scientific advice. Overall, the clinical and statistical relevance of the equivalence margin for s-CTX is difficult to justify, and the chosen margin between 80% and 125% is conventional for bioequivalence analyses. As not a substantial part of the confidence interval lies towards the extremes of the acceptance criteria and historical s-CTX data in the target population (women with PMO) is limited, this is acceptable. For the primary PD outcome unity was not included in the 95% CI, but

being clearly within the acceptance range, i.e. results were statistically significant different, but observed differences are considered clinically irrelevant. This issue is therefore not pursued further.

For the primary efficacy endpoint % change in ls-BMD, an ANCOVA analysis with the fixed effect of treatment and age, baseline BMD T-score at the lumbar spine, and prior bisphosphonates therapy (Yes versus No) as covariates was used.

No estimands or ICEs are mentioned in any of the documents submitted, but it can be assumed that a treatment policy strategy was applied for treatment discontinuation before week 26 together, use of prohibited drugs, non-drug intervention and AEs affecting bone (Fractures at lumbar spine, Fractures at Total Hip, Fractures at Femoral Neck and Non-fracture Disorders) and changes in concomitant medication. 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 randomised treatment or use of another medication for reasons that are unrelated to the similarity of the initially randomised treatments.

For the primary efficacy analysis, the ICEs of treatment discontinuation before week 26, use of prohibited drugs and AEs affecting Bone (Fractures at lumbar spine, Fractures at Total Hip, Fractures at Femoral Neck and Non-fracture Disorders) and changes in concomitant medication were compared between treatment arms from Baseline to Week 52**.**

A treatment policy strategy would reflect clinical practice whereas a hypothetical strategy may be the most sensitive approach to detect any differences that are attributable to the pharmacological action and should be included as supplementary analysis. Three statistical analyses on the primary efficacy endpoint under a hypothetical strategy (MMRM, WOCF, tipping point analysis) were provided. The results of these are in general in line with a conclusion of biosimilarity.

For the primary PD analysis, the ICEs of use of prohibited drugs and changes in concomitant medication were compared between treatment arms from Baseline to Week 26. A treatment policy strategy is applied for these intercurrent events as they might not affect the PD, i.e. data collected after ICEs were used. As study drug was only administered once for the primary PD endpoint, study drug discontinuation is irrelevant for the comparison of s-CTX at Week 26.

For a hypothetical strategy for intercurrent events, the applicant imputed PD data after intercurrent events with the possibility to influence s-CTX/P1NP and for missing PD data within the same treatment group using a multiple imputation model and performing a tipping point analysis.

The impact of missing data on primary efficacy results is evaluated under missing at random (MAR) scenario using mean imputation as well as missing not at random (MNAR) scenario using a tipping point analysis shifting the mean imputation values. These analyses are not considered appropriate. For missing data, multiple imputation or imputation by MMRM would be more appropriate than single value imputation. The applicant provided the MMRM analysis using a treatment policy strategy for intercurrent events and a tipping point analysis.

The analysis of co-primary PD endpoint was based on the set of subjects who had s-CTX measurement at Week 26 (complete case analysis). This approach assumes MCAR, i.e. that, with respect to s-CTX AUEC, patients that did not provide Week 26 s-CTX were not different from those who did. The ANCOVA on log-transformed s-CTX AUEC data with treatment as a fixed effect, age, baseline BMD T-score at the lumbar spine, prior bisphosphonates therapy (yes versus no), and baseline s-CTX level as covariates is adequate for a proportional comparison of treatment effects on bone turnover. For imputing missing PD data under MAR and MNAR, the applicant performed multiple imputation and a tipping point analysis using a treatment policy for intercurrent events.

A total of 479 patients were randomly assigned to the treatment groups for Treatment Period I (240 and 239 patients in the CT-P41 and US-Prolia groups, respectively). Of the 479 patients, 55 (11.5%) patients (18 [7.5%] and 37 [15.5%] patients in the CT-P41 and US-Prolia groups, respectively) discontinued the study treatment and 48 (10.0%) patients terminated the study participation (17 [7.1%] patients in the CT-P41 group and 31 [13.0%] patients in the US-licensed Prolia group) in treatment period 1. The difference was mainly caused by higher withdrawal by patient/lost to follow up rate in US-Prolia group (27 patients compared to 8 in CT-P41 group). In the safety set 94.1% of patients in the CT-P41 and 89.9% of patients in the US-Prolia group were administered a second dose at Week 26. Treatment discontinuations after administering the second dose are seen as irrelevant for the primary efficacy analysis. Some imbalances between groups in the numbers of discontinuation were observed being higher in US-Prolia group. This may be considered a chance finding unless an association is found between withdrawals and efficacy or safety/tolerability outcomes. Within the procedure, the applicant was requested to reason these disbalances in more detail and to clarify and analyse whether any correlation between the withdrawals and efficacy or association with safety/tolerability was present**.** Based on the applicants response, the main reason for the treatment discontinuation, and the difference between treatment groups therein, was patient's decision. However, no data were provided on the objective efficacy measures among those that withdrew prematurely. The applicant states that if treatment discontinuation was decided due to an issue related to efficacy, then disease progression would have been selected as primary reason of treatment discontinuation. This is not necessarily true; having initiated a treatment with the expectation to gain approximately +5% BMD over a year, the patient and the treating physician might question treatment continuation after 6 months if BMD is not on the expected trajectory (e.g., has not changed from baseline). Such a situation would not necessarily be recorded as "disease progression" that happened on a specific "date of progression". However, the sensitivity analysis data showed no impact of discontinuations on the interpretation of the similarity in efficacy outcome. Therefore, the issue is not pursued further.

The rate of significant protocol deviation or adverse events as causative reason for discontinuation was approximately the same between groups. Five patients in each compared treatment groups had major protocol deviation in TPI. The reason was receiving prohibited medication in all except two patients who were non-adherent to inclusion/exclusion criteria in the CT-P41. Tabulated data of all protocol deviations, also from those which did not lead to the exclusion, was missing, but this issue is not pursued further.

Overall, 39 patients and 103 visits were affected by war in Ukraine. It is understood that the dire situation in the Ukraine endures the performance of a clinical study enormously. However, in the light of a solid assessment of the suitability of CT-P41 for market authorisation, additional information was considered necessary. The applicant provided a concise overview/discussion concerning visit window violations and missed study visits for study CT-P41 3.1. Frequencies of OOW visits and missed visits were overall comparable between treatment groups. No concern arises regarding visit window violations or missed visits. The applicant also clarified 10 out of 39 patients (TPI: 6/239 [2.5%] and 4/238 [1.7%] in the CT-P41 and US-licensed Prolia groups, respectively) were excluded from PPS with either missing BMD assessment or omitted study drug administration. Additionally, 1 affected patient was excluded from PPS for other reason (due to the missing BMD assessment at Week 52, the visit not affected by the war). Nine out of 10 patients excluded from the PPS set had missing the W52 LS-BMD measurement, and in one patient the only reason for exclusion from PPS population was not administered full dose between W0 and W26. The applicant clarifies the proportion of patients being excluded from the analysis set (PPS only) to have been similar between treatment groups.

The applicant has provided the required sensitivity analysis by excluding patients having treatment discontinuation as well as patients with delayed/omitted study treatment administration or study

assessments due to coronavirus disease of 2019 (COVID-19) or the war in Ukraine. The patients who discontinued the study treatment after Week 26 were not excluded since the primary efficacy analysis was based on Week 52 pre-dose data and the primary PD analysis included data up to Week 26 pre-dose (no further dose between Weeks 26 and 52). Based on the "modified PPS analysis", the LS mean difference between compared groups for %cfb in LS-BMD at Week 52 with 95% confidence intervals (CIs) was -0.292 (-1.041, 0.458). Based on the "modified PPS analysis" for the co-primary PD endpoint, the geometric LS mean ratio for the s-CTX area under the effect curve (AUEC) over the initial 6 months with 95% CIs was 94.77 (89.97, 99.82), being within the predefined equivalence margin and in line with the initial analysis outcome for co-primary PD endpoint. The data provided does not change the original interpretation of the confirmatory efficacy and safety study outcome and confirms similarity between treatments.

The applicant has given more detailed data on out of window visits and missing visits. According to the applicant, in TP I the highest number of OOW occurred was Week 27 in both groups (41 [17.1%] visits in CT-P41 group and 50 [20.9%] visits in US-licensed Prolia group) followed by Week 26 (39 [16.3%] visits in CT-P41 group and 36 [15.1%] visits in US-licensed Prolia group). The average period of visits with occurred OOW was 8.7 days for the CT-P41 group and 8.3 days for the US-licensed Prolia group. The applicant clarifies no specific patterns were shown and trends were similar between the treatment groups. Based on the provided information, the frequency of the OOW events and missing data in each visit time point at TP I seems to equally distribute between visits being also true for TP II. The number of patients with missing value in percent change from baseline in BMD of lumbar spine at Week 52 for the CT-P41 and US-licensed Prolia groups was 43 patients (17 [7.1%] and 26 [10.9%] patients, respectively). Therefore, 5 patients in the US-licensed Prolia group terminated the study at the end of treatment period 1. Among those who initiated Treatment Period I, 422 patients were randomly assigned in Treatment Period II (221, 100 and 101 patients in the CT-P41 Maintenance, US-Prolia Maintenance and Switched to CT-P41 groups, respectively). Nine patients were not subject to perform the 2nd randomisation in Treatment Period II since they had already discontinued the study treatment in Treatment Period I.

Efficacy data and additional analyses

The percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52 was 4.9317 for the CT-P41 group and 5.0706 for the US-Prolia group in FAS population. The LS mean difference between the groups was -0.139 (95% CI -0.826, 0.548) being clearly within the pre-specified equivalence range of ±1.503% and meeting the criteria for the primary efficacy endpoint. Furthermore, the acceptance criterion for the primary endpoint were also met in PPS population with the difference between the groups being -0.280 (95% CI -0.973, 0.414). Thus, the biosimilarity criterion for the primary efficacy endpoint was met.

In FAS, Week 52 LS-BMD change from baseline was available for 222 and 212 patients (CT P41 and US-Prolia, respectively) and 215 and 202 patients in PPS. This implies that from all participants with observed primary efficacy endpoint, in total 7 and 10 were excluded from PPS (8 due to prohibited medication, 2 due inc/exc criteria), while the remaining 7 exclusions were due to not having received study medication at Week 26.

Major protocol deviations were identified prior to database lock and were discussed during the blinded DRM. They were defined as mis-randomisation, non-adherence to inclusion or exclusion criteria, significant GCP non-compliance and receiving any prohibited therapy which affected primary result. The prohibited medications which were started before the date of lumbar spine BMD assessment at Week 52 affected 27 patients. The proportion of patients who received at least 1 prohibited medication before the Week 52 DXA assessment date for lumbar spine was 16 [6.7%] in the CT-P41 group and 11 [4.6%] in the US-licensed Prolia group. Overall, 9 patients (4 and 5 patients in the CT-P41 and US-

licensed Prolia groups, respectively) were found as having a major protocol deviation related to the prohibited medication which affects the primary result and were excluded from the PPS, but 8 of these 9 patients were included in the FAS. Other reasons for the exclusion from the PPS were full dose not administered at Week 0 or Week 26 and no BMD assessment for lumbar spine at baseline or Week 52.

The number of patients with missing values was 43 (17 [7.1%] patients in CT-P41 group and 26 [10.9%] patients in US-licensed Prolia group). The following sensitivity analyses for missing data were performed: Imputing missing primary efficacy data under MAR using mean imputation and multiple imputation together with corresponding tipping point analyses for imputing under MNAR. The primary efficacy analysis seems robust concerning different assumptions for missing data. Per CHMP request, the applicant conducted an analysis that provides an estimate the treatment difference in the ITT sense: Week 52 % CfB in BMD were multiple imputed using linear regression model. These imputed %CfB values were subsequently shifted downwards, in each group, to reflect the expectation that missed denosumab dose at Week 26 would have a negative impact on BMD trajectory. Even when considering the possibility that treatment discontinuation would have a different impact depending on whether US-Prolia or CT-P41 was discontinued, a shift as high as +10 (%CfB in BMD) in one group and no shift in the other is required to question the conclusion on equivalence. It is very unlikely that the conclusion of equivalence would have been any different had all randomised patients been assessed for Week 52 BMD regardless of treatment discontinuation.

Concerning intercurrent events, 41 (17.2%) patients in the CT-P41 group and 47 (19.7%) patients in the US-licensed Prolia group had at least one intercurrent event. There were almost twice as many treatment discontinuations before week 26 in the US-licensed Prolia group than in the CT-P41 group (5.9% vs 10.1%). Treatment Discontinuation before Week 26 means subjects do not take the 2nd dose on week 26. Treatment Discontinuation after Week 26 should not affect the primary outcome at Week 52. Slightly more patients used prohibited drugs in the CT-P41 group than in the US-licensed Prolia group (6.7% vs 4.6%). Adverse events affecting bone (5.4% vs 5.0%) and changes in concomitant medication (2.5% vs 2.5%) occurred similarly often. All sensitivity analyses corresponding to a hypothetical scenario where intercurrent events did not occur showed robustness of the conclusion of equivalence. The co-primary PD endpoint "AUEC after first dose of %CfB in serum CTX" is discussed in the Clinical Pharmacology section.

In the descriptive statistics for the secondary endpoints in the FAS, the mean LS-BMD at week 26 was 0.7730 g/cm3 for the CT-P41 group and 0.7714 g/cm3 for the US-Prolia group. The mean %CfB at Week 26 was 3.7945% for the CT-P41 group and 3.4845% for the US-Prolia group. The data showed similar improvement in BMD between the compared groups. The result supported the primary endpoint outcome conclusion. The data for the mean change at Week 78 was 0.7953 (6.8588% from baseline) and 0.7923 (6.5745%), respectively, in the two compared groups. Based on these results the level of improvement remained closely similar in all groups in the maintenance phase and no meaningful difference to switch group was present.

Additional secondary endpoints were the total hip and femoral neck BMD and %cfb at week 26, 52, and 78. The data showed comparable improvement in BMD between CT-P41 and US-Prolia groups in different evaluation timepoints and also maintenance of the improvement at Week 78 with no meaningful difference to the switched group.

The secondary endpoint incidence of new fractures showed only 1 new vertebrate fracture in single patient in each compared group. Since the efficacy analysis included only vertebral fractures which occurred from T4 to L4 and were confirmed by the central imaging vendor, there were 2 vertebral fractures which were not included in the efficacy analysis. Two patients in CT-P41 group (3 events) and 4 in US-Prolia group (4 events) experience new non-vertebrate fracture. There was no hip fracture reported during Treatment Period I. A total of 9 images were not included in the efficacy analysis. Out

of 9 images, 6 images were not assessable or were confirmed by the central imaging vendor as no fracture. The rest of 3 images with the confirmation of fracture from the central imaging vendor were not included in the efficacy analysis since the fracture location was not associated with decreased BMD or was associated with severe trauma.

In the maintenance phase (treatment period 2), 1 patient in CT-P41 Maintenance group had new - vertebrate fracture, 2 patients in the CT-P41 Maintenance group (3 events) had new non-vertebrate fractures and 1 patient in the switched to CT-P41 group (1 event) had non-vertebrate fracture, there was no hip fractures reported. There were 3 images which were not included in the efficacy analysis since the fracture location was not associated with decreased BMD or the image was confirmed as no fracture by the central imaging vendor. A foot fracture (PT) in the switched to CT-P41 group was also not included in the efficacy analysis since any images or reports for the fracture were not submitted to the central imaging vendor. For majority of patients, no shift was noted in the semi-quantitative grade for vertebral fractures at Week 78 compared to baseline. Overall, the frequency of new fractures remained very low and based on the data no meaningful difference between groups can be derived. In the secondary QoL endpoints (change from baseline in health-related quality of life and EuroQoL-5 Dimensions-5 Levels Health Survey at Weeks 26, 52, and 78), the outcome improved somewhat in physical function and back pain in the CT-P41 groups by OPAC-SV score, but got slightly worse in emotional status in comparison to the US-Prolia Week 52 data. Overall, all the changes and differences between groups were minimal in health-related quality of life and have no significance on overall interpretation of the efficacy outcome. In EuroQoL-5 Dimensions-5 Levels Health Survey, the mean EQ-5D-5L index value and EQ VAS were comparable between groups with small negligent changes to the baseline being present. In the switch group small negligent improvement at Week 78 from the US-Prolia Week 52 data was observed.

In summary, the descriptive secondary endpoint data do not change the overall conclusion on the similarity in efficacy between the compared treatment arms.

2.5.7. Conclusions on the clinical efficacy

The acceptance criterion for the primary efficacy analysis, %CfB in LS-BMD at Week 52, was met with the 95% CI of the difference between the CT-P41 and the US-Prolia group being within the pre-specified acceptance range with clear margin in both FAS and PPS populations. The secondary efficacy endpoints supported the biosimilarity claim.

In conclusion, the provided efficacy data support the biosimilarity of CT-P41 and US-Prolia.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

Exposure data are available for the following studies and populations:

- Study CT-P41 1.1 (pilot study): a Phase 1, randomised, double-blind, two-arm, parallel group, single-dose study to collect preliminary safety data prior to initiation of Study CT-P41 1.2 and to evaluate the additional immunogenicity, PK and PD of CT-P41 compared to that of EU-approved Prolia (hereafter referred to as EU-Prolia) in healthy male subjects. Overall, 32 subjects were randomised, and 2 (6.3%) subjects discontinued from the study before study drug administration The Safety Set included a total of 30 subjects (15 subjects in each of CT-P41 and EU-Prolia group).

- Study CT-P41 1.2 (pivotal PK study): a Phase 1, randomised, double-blind, two-arm, parallel group, single dose study to evaluate the PK similarity in terms of area under the concentration-time curve from time zero to infinity (AUC0-inf), area under concentration- time curve from time zero to the last quantifiable concentration (AUC0-last), and maximum serum concentration (Cmax) between CT-P41 and US-Prolia in healthy male subjects. In addition, additional PK, PD, safety and immunogenicity of CT-P41 and US-Prolia were evaluated. The Safety Set included a total of 151 subjects (74 subjects in the CT-P41 group and 77 subjects in the US-Prolia group).
- Study CT-P41 3.1 (comparative efficacy and safety study): a Phase 3, randomised, double- blind, active-controlled study in postmenopausal women with osteoporosis, which was designed to demonstrate therapeutic equivalence of CT-P41 and US-licensed Prolia (hereafter referred to as US-Prolia) determined by percent change from baseline in bone mineral density (BMD) for lumbar spine (L1 to L4) at Week 52 and to compare other efficacy, PK, PD, safety and immunogenicity. The Safety Set included a total of 477 postmenopausal osteoporosis (PMO) patients (239 patients in the CT-P41 group and 238 patients in the US-Prolia group).

No studies were conducted with the reference product Xgeva as comparator.

The Safety Set was defined as all subjects who received at least one dose (full or partial) of either of the study drugs (CT-P41 or EU-Prolia/US-Prolia). Subjects were analysed based on the treatment received in each treatment period.

Table 27. Number of subjects who received at least 1 dose of study drug (CT-P41 or Prolia) in the CT-P41 clinical studies: safety set

Study	Subjects	Amount of Exposure	Number of Subjects who Received ≥ 1 Dose of Study Drug			
			CT-P41 Only	Prolia Only*	Prolia/ CT-P41**	Total
CT-P41 3.1	PMO Patients	At least 1 dose	239	137	101	477
		Total 3 doses	220	100	101	421
CT-P41 1.2	Healthy Subjects	Single dose	74	77	-	151
CT-P41 1.1		Single dose	15	15	-	30
Total		**At least 1 dose**	328	229	101	658

*US-Prolia for Study CT-P41 3.1 and Study CT-P41 1.2. EU-Prolia for Study CT-P41 1.1. ** In Study CT-P41 3.1, 101 patients who were exposed to US-Prolia during TP1 switched to CT-P41 for TP2 after a single transition. Abbreviations: PMO, postmenopausal women with osteoporosis; TP1, Treatment Period I; TP2, Treatment Period II

2.5.8.2. Adverse events

1) Adverse events and drug reactions in healthy male population

Study CT-P41 1.1

Fifteen (100.0%) subjects in each treatment group received the whole volume of a 60 mg dose of CT-P41 or EU-approved Prolia.

Treatment-emergent adverse events (TEAEs) were reported for 6/15 (40.0%) and 12/15 (80.0%) subjects in the CT-P41 and EU-Prolia groups, respectively (Table 28). The most frequently reported TEAEs by SOC were nervous system disorders (2/15 [13.3%] and 5/15 [33.3%] subjects, respectively) and musculoskeletal and connective tissue disorders (1/15 [6.7%] and 5/15 [33.3%] subjects, respectively) and by PT was headache (1/15 [6.7%] and 3/15 [20.0%] subjects, respectively).

Overall, 18/30 (60.0%) subjects (6/15 [40.0%] in the CT-P41 treatment group and 12/15 [80.0%] in the EU-approved Prolia treatment group) experienced at least 1 TEAE.

TEAEs considered related to the study drug by the investigator were reported in 9/15 (30.0%) subjects: 3/15 subjects [20.0%] in the CT-P41 treatment group (incl. the AEs: nasopharyngitis, muscle discomfort, myalgia, and headache, 1 of each) and 6/15 subjects (40.0%) in the EU-approved Prolia treatment group (incl. the AEs: abdominal pain, diarrhoea, injection site bruising, RSV infection, tooth infection, hypocalcaemia, arthralgia, bone pain, headache, 1 of each). Severity of all reported AEs were of Grade 1, except the tooth infection was Grade 2.

Hence, in the pilot study CT-P41 1.1, both TEAEs and TEAEs considered related to the study drug by the investigator were reported twice as often in the EU-approved Prolia treatment group than in the CT-P41 group. The different (more favourable) safety profile of CT-P41 vs. EU-Prolia in the small pilot study could be due to chance instead of true difference, taking in account the similar PK/PD of CT-P41 vs. EU- and US-Prolia, and similar safety profile of CT-P41 vs. US-Prolia in the larger studies CT-P41 1.2 and CT-P41 3.1.

Table 28. Overall summary of adverse events (study CT-P41 1.1)

	CT-P41 (N=15)	EU-approved Prolia (N=15)	Overall (N=30)
Total number of AEs	9	26	35
Total number of SAEs	0	0	0
Total number of TEAEs	9	25	34
Number of subjects with at least 1 AE	6 (40.0)	13 (86.7)	19 (63.3)
Number of subjects with at least 1 SAE	0	0	0
Number of subjects with at least 1 TEAE	6 (40.0)	12 (80.0)	18 (60.0)
Number of subjects with at least 1 TESAE	0	0	0
Number of subjects with at least 1 TEAE leading to study discontinuation	0	0	0
Number of subjects with at least 1 TEAE leading to death	0	0	0
Number of subjects with at least 1 TEAE classified as hypersensitivity/allergic reaction	0	0	0
Number of subjects with at least 1 TEAE classified as infection	2 (13.3)	3 (20.0)	5 (16.7)
Number of subjects with at least 1 TEAE classified as hypocalcaemia	0	1 (6.7)	1 (3.3)
Number of subjects with at least 1 TEAE classified as ONJ	0	0	0

Abbreviations: AE, adverse event; EU, European Union; ONJ, osteonecrosis of jaw; SAE, serious adverse event; TEAE, treatment-emergent AE; TESAE, treatment-emergent SAE.
Note: Each subject could only contribute once to each of the incidence rates, regardless of the number of occurrences.

Study CT-P41 1.2

All 151 (100.0%) subjects in the Safety Set received the whole volume of a 60 mg dose of either CT-P41 or US-licensed Prolia.

An overall summary of TEAEs is presented for the Safety Set in Table 29. Overall, 282 TEAEs were reported from 114/282 (75.5%) subjects (55/74 [74.3%] and 59/77 [76.6%] subjects in the CT-P41 and US-licensed Prolia treatment groups, respectively). There were no TESAEs and TEAEs leading to study discontinuation.

Table 29. Overall summary of adverse events (study CT-P41 1.2)

	CT-P41 (N=74)	US-licensed Prolia (N=77)	Total (N=151)
Total number of TEAEs	**135**	**147**	**282**
Number (%) of subjects with at least 1 TEAE	55 (74.3)	59 (76.6)	114 (75.5)
Related to the study drug	39 (52.7)	45 (58.4)	84 (55.6)
Unrelated to the study drug	41 (55.4)	43 (55.8)	84 (55.6)
Total number of TESAEs	**0**	**0**	**0**
Total number of TEAEs leading to study drug discontinuation	**0**	**0**	**0**
Total number of TEAEs classified as ISR	**2**	**0**	**2**
Number (%) of subjects with at least 1 TEAE classified as ISR	2 (2.7)	0	2 (1.3)
Related to the study drug	2 (2.7)	0	2 (1.3)
Unrelated to the study drug	0	0	0
Total number of TEAEs classified as drug-related hypersensitivity/allergic reactions	**0**	**0**	**0**
Total number of TEAEs classified as infection	**19**	**26**	**45**
Number (%) of subjects with at least 1 TEAE classified as infection	18 (24.3)	22 (28.6)	40 (26.5)
Related to the study drug	4 (5.4)	7 (9.1)	11 (7.3)
Unrelated to the study drug	14 (18.9)	18 (23.4)	32 (21.2)
Total number of TEAEs classified as hypocalcaemia	**0**	**0**	**0**

Abbreviations: ISR; injection site reaction, TEAE, treatment-emergent adverse event; TESAE, treatment- emergent serious adverse event; US, United States.
Note: At each level of summarisation, a subject was counted once if they reported one or more AEs, and only the most severe event was counted. The event was considered related if the relationship was defined as 'Possible,' 'Probable,' and 'Definite.'

TEAEs classified as injection site reactions (ISRs) were reported from 2 (1.3%) subjects (2 [2.7%] subjects in the CT-P41 treatment group only).

TEAEs classified as infection were reported from 40/151 (26.5%) subjects (18/74 [24.3%] and 22/77 [28.6%] subjects in the CT-P41 and US-licensed Prolia treatment groups, respectively). TEAEs classified as drug-related hypersensitivity/allergic reactions and hypocalcaemia were not reported during the study. However, events with PT Blood calcium decreased were reported. These TEAEs were reported when the total calcium level was lower than 8.5 mg/dL, which was a set criterion considered by the investigators to be clinically significantly abnormal. Except for 1 case which reported for active observation (in the US-Prolia group with total calcium level was 8.3 mg/dL on Day 8, returned to normal on next visit), all other cases were reported that the event did not involve any clinical signs and symptoms related to decreased total calcium level below 8.5 mg/dL. All the blood calcium decreased cases were grade 1 (mild) or grade 2 (moderate) in intensity and did not require any treatment for the AEs.

Table 30. Treatment-emergent adverse events reported for ≥ 3% of subjects in either treatment group by preferred term: safety set (study CT-P41 1.2)

CT-P41		US-licensed Prolia	Total
Preferred Term, n (%) (N=74)		**(N=77)**	**(N=151)**
Blood calcium decreased	28 (37.8)	35 (45.5)	63 (41.7)
COVID-19	8 (10.8)	7 (9.1)	15 (9.9)
Nasopharyngitis	6 (8.1)	8 (10.4)	14 (9.3)
Alanine aminotransferase increased	6 (8.1)	4 (5.2)	10 (6.6)
Blood triglycerides increased	5 (6.8)	5 (6.5)	10 (6.6)
Low density lipoprotein increased	3 (4.1)	6 (7.8)	9 (6.0)
Coronavirus infection	2 (2.7)	6 (7.8)	8 (5.3)
Aspartate aminotransferase increased	3 (4.1)	2 (2.6)	5 (3.3)
Arthralgia	3 (4.1)	2 (2.6)	5 (3.3)
Blood bilirubin increased	1 (1.4)	3 (3.9)	4 (2.6)
Blood creatine phosphokinase increased	3 (4.1)	0	3 (2.0)
Paraesthesia	3 (4.1)	0	3 (2.0)

Abbreviations: COVID-19, coronavirus disease 2019; US, United States.
Note: At each level of summarisation, a subject was counted once if they reported one or more AEs, and only the most severe event was counted.

Adverse events of special interest (AESI)

AESI were defined as follows:

For CT-P41 1.1: hypersensitivity/allergic reactions, infection, hypocalcaemia and ONJ

For CT-P41 1.2: injection site reaction, drug-related hypersensitivity/allergic reaction, infection and hypocalcaemia

Study CT-P41 1.1

Regarding the treatment-emergent adverse events of special interest (TEAESI), TEAEs of infection were reported for 2/15 [13.3%] subjects in the CT-P41 treatment group (1 RSV infection and 1 nasopharyngitis) and 3/15 [20.0%] subjects in the EU-Prolia treatment group (tooth infection, gastroenteritis and RSV infection).

TEAEs of hypocalcaemia were reported in only one subject: 1/15 subjects in the EU-Prolia treatment group (grade 1 in intensity).

TEAEs classified as hypersensitivity/allergic reaction and ONJ were not reported.

There were no TESAEs or TEAEs leading to study discontinuation. There were no deaths.

Study CT-P41 1.2

TEAEs of special interest were reported as follows:

- 2/74 [2.7%] subjects in the CT-P41 treatment group only with reported TEAEs classified as injection site reaction (ISR), related to study drug, grade 1 in intensity,
- No TEAEs classified as drug-related hypersensitivity/allergic reactions,

- Overall, 40/151 (26.5%) subjects (18/74 [24.3%] and 22/77 [28.6%] subjects in the CT-P41 and US- Prolia treatment groups, respectively) experienced at least 1 TEAE classified as infection; all grade 1 or 2 in intensity. There is no imbalance in occurrence of infections between study groups.
- No TEAEs classified as hypocalcaemia were reported.

There were no deaths, TESAEs, or TEAEs leading to study discontinuation.

2) Adverse events and drug reactions in patients with postmenopausal osteoporosis

Study CT-P41 3.1

For PMO patients, TEAEs reported for the Overall Period are described according to relatedness in Tables 3.3.7.2.2.1. Overall, 376 (78.8%) patients experienced at least 1 TEAE and the proportions were similar among groups (193 [80.8%] and 183 [76.9%] patients in the CT-P41 and US-licensed Prolia group, respectively; and 177 [80.5%], 75 [75.0%], and 82 [81.2%] patients in the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups, respectively).

During TP I, five subjects in both CT-P41 and US-Prolia group discontinued study drug due to TEAE, and during TP II there were no discontinuations due to TEAE. Numbers of adverse events TESAEs were low and none of the TESAEs was considered related to study drug.

An overview of all TEAEs by PT Reported for at Least 3% of Patients in Any Treatment Group by SOC and PT in Study CT-P41 3.1 are provided in Table 31.

Regarding adverse events of special interest (AESI), there was a difference in incidence of infections that is discussed later in this AR.

Table 31. Overview of treatment-emergent adverse events in study CT-P41 3.1 (overall period): safety set

	CT-P41 (N=239)	US-licensed Prolia (N=238)	CT-P41 Maintenance (N=220)	US-licensed Prolia Maintenance (N=100)	Switched to CT-P41 (N=101)	Total (N=477)
Total number of TEAEs	**802**	**739**	**745**	**301**	**338**	**1541**
Number (%) of patients with at least 1 TEAE	193 (80.8%)	183 (76.9%)	177 (80.5%)	75 (75.0%)	82 (81.2%)	376 (78.8%)
Related to the study drug	55 (23.0%)	49 (20.6%)	50 (22.7%)	19 (19.0%)	20 (19.8%)	104 (21.8%)
Unrelated to the study drug	184 (77.0%)	179 (75.2%)	169 (76.8%)	72 (72.0%)	81 (80.2%)	363 (76.1%)
Total number of TESAEs	**17**	**18**	**14**	**10**	**5**	**35**
Number (%) of patients with at least 1 TESAE	14 (5.9%)	13 (5.5%)	12 (5.5%)	8 (8.0%)	2 (2.0%)	27 (5.7%)
Related to the study drug	0	0	0	0	0	0
Unrelated to the study drug	14 (5.9%)	13 (5.5%)	12 (5.5%)	8 (8.0%)	2 (2.0%)	27 (5.7%)
Total number of TEAEs leading to discontinuation of study drug	**5**	**6**	**0**	**0**	**0**	**11**
Number (%) of patients with at least 1 TEAE leading to discontinuation of study drug	5 (2.1%)	5 (2.1%)	0	0	0	10 (2.1%)
Related to the study drug	0	2 (0.8%)	0	0	0	2 (0.4%)
Unrelated to the study drug	5 (2.1%)	3 (1.3%)	0	0	0	8 (1.7%)
Total number of TEAEs classified as injection site reactions	**8**	**4**	**8**	**0**	**2**	**12**
Number (%) of patients with at least 1 TEAE classified as injection site reactions	8 (3.3%)	4 (1.7%)	8 (3.6%)	0	2 (2.0%)	12 (2.5%)
Related to the study drug	8 (3.3%)	4 (1.7%)	8 (3.6%)	0	2 (2.0%)	12 (2.5%)
Unrelated to the study drug	0	0	0	0	0	0

Total number of TEAEs classified as drug-related hypersensitivity/allergic reaction	**1**	**2**	**1**	**1**	**1**	**3**
Number (%) of patients with at least 1 TEAE classified as drug-related hypersensitivity/allergic reaction	1 (0.4%)	2 (0.8%)	1 (0.5%)	1 (1.0%)	1 (1.0%)	3 (0.6%)
Related to the study drug	1 (0.4%)	2 (0.8%)	1 (0.5%)	1 (1.0%)	1 (1.0%)	3 (0.6%)
Unrelated to the study drug	0	0	0	0	0	0
Total number of TEAEs classified as infections	**180**	**159**	**165**	**62**	**81**	**339**
Number (%) of patients with at least 1 TEAE classified as infections	111 (46.4%)	90 (37.8%)	102 (46.4%)	36 (36.0%)	47 (46.5%)	201 (42.1%)
Related to the study drug	5 (2.1%)	1 (0.4%)	5 (2.3%)	0	1 (1.0%)	6 (1.3%)
Unrelated to the study drug	107 (44.8%)	90 (37.8%)	98 (44.5%)	36 (36.0%)	47 (46.5%)	197 (41.3%)
Total number of TEAEs classified as hypocalcaemia	**11**	**8**	**10**	**3**	**3**	**19**
Number (%) of patients with at least 1 TEAE classified as hypocalcaemia	8 (3.3%)	7 (2.9%)	7 (3.2%)	3 (3.0%)	3 (3.0%)	15 (3.1%)
Related to the study drug	5 (2.1%)	5 (2.1%)	4 (1.8%)	2 (2.0%)	2 (2.0%)	10 (2.1%)
Unrelated to the study drug	4 (1.7%)	2 (0.8%)	4 (1.8%)	1 (1.0%)	1 (1.0%)	6 (1.3%)
Total number of TEAEs classified as ONJ	**0**	**1**	**0**	**0**	**0**	**1**
Number (%) of patients with at least 1 TEAE classified as ONJ	0	1 (0.4%)	0	0	0	1 (0.2%)
Related to the study drug	0	1 (0.4%)	0	0	0	1 (0.2%)
Unrelated to the study drug	0	0	0	0	0	0
Total number of TEAEs classified as atypical femoral fracture	**0**	**0**	**0**	**0**	**0**	**0**

Total number of TEAEs classified as dermatologic reactions	**16**	**16**	**15**	**11**	**4**	**32**
Number (%) of patients with at least 1 TEAE classified as dermatologic reactions	13 (5.4%)	13 (5.5%)	12 (5.5%)	8 (8.0%)	4 (4.0%)	26 (5.5%)
Related to the study drug	1 (0.4%)	1 (0.4%)	1 (0.5%)	1 (1.0%)	0	2 (0.4%)
Unrelated to the study drug	12 (5.0%)	12 (5.0%)	11 (5.0%)	7 (7.0%)	4 (4.0%)	24 (5.0%)
Total number of TEAEs leading to death	**2**	**0**	**1**	**0**	**0**	**2**
Number (%) of patients with TEAEs leading to death	2 (0.8%)	0	1 (0.5%)	0	0	2 (0.4%)
Related to the study drug	0	0	0	0	0	0
Unrelated to the study drug	2 (0.8%)	0	1 (0.5%)	0	0	2 (0.4%)

Abbreviations: TEAE, treatment-emergent adverse event; ONJ, osteonecrosis of the jaw; TESAE, treatment-emergent serious adverse event; US, United States. Note: The total number of TEAEs counted included events of all patients in the Safety Set. At each level of summarisation, a patient was counted once if they reported 1 or more events. The event was considered to be related if the relationship was defined as "possible", "probable", or "definite".

Table 32. TEAEs reported for ≥3% of patients presented by system organ class and preferred term (overall period): safety set

System Organ Class Preferred Term	**CT-P41 (N=239)**	**US-licensed Prolia (N=238)**	**CT-P41 Maintenance (N=220)**	**US-licensed Prolia Maintenance (N=100)**	**Switched to CT-P41 (N=101)**	**Total (N=477)**
	Number (%) of patients					
Total number of TEAEs reported for at least 3%	**331**	**326**	**312**	**146**	**145**	**657**
Blood and lymphatic system disorders	**5 (2.1%)**	**10 (4.2%)**	**5 (2.3%)**	**4 (4.0%)**	**5 (5.0%)**	**15 (3.1%)**
Neutropenia	0	4 (1.7%)	0	3 (3.0%)	1 (1.0%)	4 (0.8%)
Thrombocytopenia	5 (2.1%)	7 (2.9%)	5 (2.3%)	2 (2.0%)	4 (4.0%)	12 (2.5%)
Endocrine disorders	**7 (2.9%)**	**2 (0.8%)**	**7 (3.2%)**	**0**	**2 (2.0%)**	**9 (1.9%)**
Goitre	7 (2.9%)	2 (0.8%)	7 (3.2%)	0	2 (2.0%)	9 (1.9%)
Gastrointestinal disorders	**10 (4.2%)**	**13 (5.5%)**	**9 (4.1%)**	**5 (5.0%)**	**5 (5.0%)**	**23 (4.8%)**
Constipation	8 (3.3%)	9 (3.8%)	7 (3.2%)	5 (5.0%)	1 (1.0%)	17 (3.6%)

Gastroesophageal reflux disease	3 (1.3%)	4 (1.7%)	3 (1.4%)	0	4 (4.0%)	7 (1.5%)
General disorders and administration site conditions	**8 (3.3%)**	**4 (1.7%)**	**8 (3.6%)**	**0**	**2 (2.0%)**	**12 (2.5%)**
Injection site reaction	8 (3.3%)	4 (1.7%)	8 (3.6%)	0	2 (2.0%)	12 (2.5%)
Infections and infestations	**85 (35.6%)**	**74 (31.1%)**	**77 (35.0%)**	**32 (32.0%)**	**38 (37.6%)**	**159 (33.3%)**
COVID-19	36 (15.1%)	35 (14.7%)	33 (15.0%)	18 (18.0%)	17 (16.8%)	71 (14.9%)
Nasopharyngitis	13 (5.4%)	17 (7.1%)	11 (5.0%)	9 (9.0%)	8 (7.9%)	30 (6.3%)
Upper respiratory tract infection	36 (15.1%)	32 (13.4%)	35 (15.9%)	11 (11.0%)	17 (16.8%)	68 (14.3%)
Urinary tract infection	17 (7.1%)	7 (2.9%)	15 (6.8%)	1 (1.0%)	6 (5.9%)	24 (5.0%)
Injury, poisoning and procedural complications	**3 (1.3%)**	**4 (1.7%)**	**3 (1.4%)**	**3 (3.0%)**	**1 (1.0%)**	**7 (1.5%)**
Tooth fracture	3 (1.3%)	4 (1.7%)	3 (1.4%)	3 (3.0%)	1 (1.0%)	7 (1.5%)
Investigations	**5 (2.1%)**	**9 (3.8%)**	**5 (2.3%)**	**6 (6.0%)**	**2 (2.0%)**	**14 (2.9%)**
Blood parathyroid hormone increased	5 (2.1%)	9 (3.8%)	5 (2.3%)	6 (6.0%)	2 (2.0%)	14 (2.9%)
Metabolism and nutrition disorders	**42 (17.6%)**	**39 (16.4%)**	**39 (17.7%)**	**19 (19.0%)**	**17 (16.8%)**	**81 (17.0%)**
Dyslipidaemia	2 (0.8%)	6 (2.5%)	1 (0.5%)	3 (3.0%)	3 (3.0%)	8 (1.7%)
Hypercalcaemia	11 (4.6%)	7 (2.9%)	11 (5.0%)	3 (3.0%)	4 (4.0%)	18 (3.8%)
Hypercholesterolaemia	8 (3.3%)	9 (3.8%)	8 (3.6%)	4 (4.0%)	3 (3.0%)	17 (3.6%)
Hyperuricaemia	5 (2.1%)	7 (2.9%)	5 (2.3%)	4 (4.0%)	3 (3.0%)	12 (2.5%)
Hypocalcaemia	8 (3.3%)	7 (2.9%)	7 (3.2%)	3 (3.0%)	3 (3.0%)	15 (3.1%)
Hypokalaemia	1 (0.4%)	3 (1.3%)	1 (0.5%)	3 (3.0%)	0	4 (0.8%)
Vitamin D deficiency	15 (6.3%)	9 (3.8%)	13 (5.9%)	4 (4.0%)	5 (5.0%)	24 (5.0%)
Musculoskeletal and connective tissue disorders	**55 (23.0%)**	**57 (23.9%)**	**52 (23.6%)**	**27 (27.0%)**	**23 (22.8%)**	**112 (23.5%)**
Arthralgia	28 (11.7%)	22 (9.2%)	26 (11.8%)	8 (8.0%)	11 (10.9%)	50 (10.5%)
Back pain	6 (2.5%)	12 (5.0%)	6 (2.7%)	5 (5.0%)	6 (5.9%)	18 (3.8%)
Osteoarthritis	12 (5.0%)	16 (6.7%)	11 (5.0%)	7 (7.0%)	6 (5.9%)	28 (5.9%)
Pain in extremity	13 (5.4%)	9 (3.8%)	13 (5.9%)	5 (5.0%)	3 (3.0%)	22 (4.6%)
Spinal osteoarthritis	3 (1.3%)	6 (2.5%)	3 (1.4%)	3 (3.0%)	1 (1.0%)	9 (1.9%)
Spinal pain	6 (2.5%)	6 (2.5%)	6 (2.7%)	3 (3.0%)	2 (2.0%)	12 (2.5%)

Nervous system disorders	**13 (5.4%)**	**16 (6.7%)**	**12 (5.5%)**	**7 (7.0%)**	**7 (6.9%)**	**29 (6.1%)**
Dizziness	6 (2.5%)	6 (2.5%)	5 (2.3%)	3 (3.0%)	3 (3.0%)	12 (2.5%)
Headache	8 (3.3%)	11 (4.6%)	8 (3.6%)	5 (5.0%)	4 (4.0%)	19 (4.0%)
Renal and urinary disorders	**3 (1.3%)**	**10 (4.2%)**	**3 (1.4%)**	**4 (4.0%)**	**5 (5.0%)**	**13 (2.7%)**
Haematuria	1 (0.4%)	6 (2.5%)	1 (0.5%)	4 (4.0%)	1 (1.0%)	7 (1.5%)
Renal cyst	2 (0.8%)	5 (2.1%)	2 (0.9%)	1 (1.0%)	4 (4.0%)	7 (1.5%)
Skin and subcutaneous tissue disorders	**5 (2.1%)**	**3 (1.3%)**	**4 (1.8%)**	**3 (3.0%)**	**0**	**8 (1.7%)**
Rash	5 (2.1%)	3 (1.3%)	4 (1.8%)	3 (3.0%)	0	8 (1.7%)
Vascular disorders	12 (5.0%)	3 (1.3%)	12 (5.5%)	1 (1.0%)	2 (2.0%)	**15 (3.1%)**
Hypertension	12 (5.0%)	3 (1.3%)	12 (5.5%)	1 (1.0%)	2 (2.0%)	15 (3.1%)

Note: Only TEAEs reported for at least 3% of patients in either group were included. At each level of summarisation, a patient was counted once if the patient reported one or more events. System organ classes and preferred terms were coded using Medical Dictionary for Regulatory Activities, Version 26.0.

Adverse events of special interest (AESI)

Adverse events of special interest (AESI) were defined in study CT-P41 3.1 as follows:

- injection site reaction,
- drug-related hypersensitivity/allergic reaction,
- infection,
- hypocalcaemia,
- osteonecrosis of the jaw (ONJ),
- atypical femoral fracture, and
- dermatologic reactions.

Except for infections, the proportions of patients who experienced treatment-emergent adverse events of special interest (TEAESIs) were similar between CT-P41 and reference product as detailed below. The pattern of TEAESIs reported in the studies comparing the safety profile of CT-P41 and reference product were consistent with the well-known safety profile and identified potential risks described in Prolia SmPC.

- **Injection site reactions (ISR)**

For the Overall period, TEAEs of injection site reaction (ISR) were reported for a total of 12 patients: 8 (3.3%) and 4 (1.7%) patients in the CT-P41 and US-licensed Prolia groups, respectively; and 8 (3.6%), 0, and 2 (2.0%) patients in the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups, respectively. The most common ISR was injection site erythema, 10 patients in total. All events were Grade 1 or 2 in severity. No action was taken with the study drug after the ISR and all patients recovered from the events without requiring medication treatment.

- **Drug-related hypersensitivity/allergic reactions**

During the Overall period, TEAEs of drug-related hypersensitivity/allergic reactions were reported for 1/239 (0.4%) patients in the CT-P41 group, 2/238 (0.8%) patients in the US-Prolia group, 1/220 (0.5%) in the CT-P41 Maintenance group, 1/100 (1.0%) patient in the US-Prolia Maintenance group and 1/101 (1.0%) patient in the Switched to CT- P41 group. Pruritus, urticaria and rash erythematous were reported as signs and symptoms of drug-related hypersensitivity/allergic reactions and all patients have recovered from the events.

- **Infections**

During the Overall Period, TEAEs of infections were reported for 111/239 (46.4%) patients in the CT-P41 group, 102/220 (46.4%) in the CT-P41 Maintenance group, 90/238 (37.8%) patients in the US-Prolia group, 36/100 (36.0%) patients in the US-Prolia Maintenance group and 47/101 (46.5%) patients in the Switched to CT-P41 group.

Infections that were considered related to the study drug were reported for 5/239 (2.1%) patients in the CT-P41 group, 5/220 (2.3%) patients in the CT-P41 Maintenance group, 1/238 (0.4%) patient in the US-Prolia group, 0 patients in the US-Prolia Maintenance group and 1/101 (1.0%) patient in the Switched to CT-P41 group. All TEAEs of infections reported during the Overall Period were considered not clinically significant as they were all mild infections with Grade 1 or 2 in severity, with only one exception of a COVID-19 case during TP1 in the US-Prolia group, which was serious and Grade 3.

Among infections by PT reported for ≥2% patients in either group, 1 event bronchitis (CT-P41 group) in TP I, 1 event of urinary tract infection (UTI) (CT-P41 Maintenance group) and 1 event of herpes zoster (Switched to CT-P41 group) in TP II were assessed by the investigator as related to the study drug.

During Treatment Period I, the number (%) of patients with ≥1 infections was 90/239 (37.7) and 67/238 (28.2) in the CT-P41 and US-Prolia groups, respectively. There were, e.g., more UTI and upper respiratory tract infections (URTI) in the CT-P41 vs. US-Prolia group, respectively. Even though URTI and UTI are listed in Section 4.8 of the SmPC of Prolia as common adverse reactions, these infections were mostly considered unrelated to study drug by investigator. There were 5/239 cases of oral herpes in the CT-P41 group and none in the US-Prolia group. Other than URTI, UTI and oral herpes, most TEAEs of infection that were reported at a higher rate in the CT-P41 group than in the US-Prolia group were reported in only one or two patients from the CT-P41 group and were considered unrelated to the study drug (data not included here for brevity). These events covered a wide range of infections in different parts of the body. Other than skin infections and serious infections, which were specifically included as precautions of use for denosumab in Section 4.4 "Special Warnings and Precautions for Use" of Prolia SmPC, the mild infections that were observed in Study CT-P41 3.1 were not described as precautions in the Prolia SmPC.

During TP I, there was one serious TEAE of infection in the US-Prolia group: Grade 3 serious COVID-19 infection, considered unrelated to the study drug. Study drug administration at Week 26 was interrupted as the patient recovered after receiving treatment of oxygen, enoxaparin sodium, dexamethasone sodium, ceftriaxone sodium and tocilizumab.

During TP II, there were more patients with TEAEs in the SOC Infections and infestations in the Switched to CT-P41 group (27/101, 26.7%) vs. the CT-P41 Maintenance (41/220, 18.6%) and US-Prolia Maintenance (18/100, 18.0%) groups. However, the difference pertains to events considered unrelated to study drug by the investigator. Specifically, there were URTI and COVID-19 cases in the Switched to CT-P41 group. UTIs occurred more frequently in the CT-P41 Maintenance group. There were no TEAEs of infection that were serious or led to study drug discontinuation during TP2.

The root cause for the imbalance in the incidence of infections in Study CT-P41 3.1 in favour of US-Prolia vs. CT-P41 was not readily obvious from the data. Therefore, detailed information for all infections and especially opportunistic infections during this study were requested to be analysed and discussed by the applicant. Patients who were at higher risk of infection (patients who reported chronic disease or diabetes, or those who were on steroids or immunosuppression) were searched by the applicant. In TPI, 38 (15.9%) and 21 (8.8%) high-risk patients in the CT-P41 and US-licensed Prolia groups, respectively, reported at least 1 infection event. A total of 59 and 41 infection events were reported from high-risk patients in each CT-P41 and US-licensed Prolia groups, respectively. Hence, more high-risk patients were identified in subjects with infections in the CT-P41 group than the US-licensed Prolia group in TP I. In TP II, however, infection incidents between treatment groups showed comparable patterns of the number of high-risk patients in TP II (17 [7.7%], 3 [3.0%], and 7 [6.9%] high-risk patients who reported at least 1 infection events in the CT-P41 Maintenance, US-licensed Prolia Maintenance, and Switched to CT-P41 groups, respectively; infection events: 18.6% vs. 18.0% vs. 26.7%).

Furthermore, upon request, the applicant analysed opportunistic infections (OIs) by assessing all patients who reported infection events. Since most infection events do not specify the exact pathogen, a conservative approach to identify the case of OIs were taken. Out of 339 infection events that occurred during the overall study period, 13 (3.8% of all events) were identified as OIs (TP I: 5 and 2 events from CT-P41 and US-licensed Prolia groups, respectively; TP II: 3, 1, and 2 events from CT-P41 Maintenance, US-licensed Prolia Maintenance, and Switched to CT-P41 groups, respectively). The reported OIs included herpes zoster, respiratory syncytial virus infection, pneumonia, vulvovaginal mycotic infection, and staphylococcal skin infection. Pneumonia is not generally classified as an OI, but it has been conservatively included due to the lack of causative pathogens information. There were no cases of TB reported in the study. All OIs were non-serious and either Grade 1 or 2 in severity.

Table 33. Summary of infection events (treatment period I and treatment period II): safety set and safety-treatment period II subset

	Treatment Period I		Treatment Period II		
Relatedness Intensity Preferred Term	**CT-P41 (N=239)**	**US-licensed Prolia (N=238)**	**CT-P41 Maintenance (N=220)**	**US-licensed Prolia Maintenance (N=100)**	**Switched to CT-P41 (N=101)**
Number (%) of patients with ≥1 infections	**90 (37.7)**	**67 (28.2)**	**41 (18.6)**	**18 (18.0)**	**27 (26.7)**
Related	3 (1.3)	0	2 (0.9)	0	1 (1.0)
Grade 1	1 (0.4)	0	0	0	1 (1.0)
Grade 2	2 (0.8)	0	2 (0.9)	0	0
Unrelated	**87 (36.4)**	**67 (28.2)**	**40 (18.2)**	**18 (18.0)**	**27 (26.7)**
Grade 1	14 (5.9)	16 (6.7)	6 (2.7)	3 (3.0)	2 (2.0)
Grade 2	73 (30.5)	50 (21.0)	34 (15.5)	15 (15.0)	24 (23.8)
Grade 3	0	1 (0.4)	0	0	0
Missing	0	0	0	0	1 (1.0)
Infection by PT reported for ≥2% patients					
Bronchitis	3 (1.3) [1]	1 (0.4)	2 (0.9)	2 (2.0)	0
COVID-19	28 (11.7)	26 (10.9)	8 (3.6)	3 (3.0)	6 (5.9)
Herpes zoster	3 (1.3)	1 (0.4)	0	0	2 (2.0) [1]
Influenza	0	0	2 (0.9)	2 (2.0)	0
Nasopharyngitis	10 (4.2)	12 (5.0)	4 (1.8)	3 (3.0)	4 (4.0)
Oral herpes	5 (2.1)	0	1 (0.5)	1 (1.0)	0
Sinusitis	1 (0.4)	1 (0.4)	1 (0.5)	0	2 (2.0)
Upper respiratory tract infection	25 (10.5)	20 (8.4)	13 (5.9)	4 (4.0)	11 (10.9)
Urinary tract infection	12 (5.0)	4 (1.7)	6 (2.7)	0	3 (3.0) [1]
Viral upper respiratory tract infection	0	1 (0.4)	0	1 (1.0)	3 (3.0)

Note: At each level of summarisation, patients are counted once if they reported one or more events.
Abbreviations: COVID-19, coronavirus disease 2019; PT, preferred term; TP, treatment period; US, United States.

- **Hypocalcaemia**

Overall, the number (%) of patients who experienced at least 1 TEAE classified as hypocalcaemia was 15 (3.1%) patients (8 [3.3%] and 7 [2.9%] patients in the CT-P41 and US-licensed Prolia groups, respectively; and 7 [3.2%], 3 [3.0%], and 3 [3.0%] patients in the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups, respectively).

No serious TEAEs classified as hypocalcaemia were reported. The TEAEs classified as hypocalcaemia considered by the investigator to be related to the study drug were reported for 10 (2.1%) patients (5 [2.1%] and 5 [2.1%] patients in the CT-P41 and US-licensed Prolia groups, respectively; and 4 [1.8%], 2 [2.0%], and 2 [2.0%] patients in the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups, respectively). All TEAEs classified as hypocalcaemia were Grade 1 in severity except for 1 Grade 2 case.

- **Osteonecrosis of Jaw**

During the study, one patient reported TEAE classified as osteonecrosis of jaw (ONJ) during TP I (in the US-Prolia group). The event was considered as possibly related to the study drug by the investigator and was non-serious Grade 2 in severity. The patient discontinued the study drug due to the event

before the administration of the study drug at Week 26 and was not recovered with medication. There were no ONJ cases in the CT-P41 group during TP I or in any treatment groups during TP II.

- **Atypical femoral fracture**

There were no atypical femoral fractures reported for Study CT-P41 3.1.

- **Dermatologic reactions**

Dermatologic reactions reported during the study are presented in Table 34. The reported events were all non-serious and Grade 1 or 2 in severity. There were 3 events considered related to study drug: granuloma annulare (1 event in the US-Prolia group), hand dermatitis (1 event in the CT-P41 group), and psoriasis (1 related event in the US-Prolia group). Events considered not related included dermatitis, dermatitis allergic, dermatitis contact, erythema, lichen planus, pruritus, psoriasis, rash, and skin lesion.

All patients recovered from the event.

Table 34. Summary of dermatologic reactions in study CT-P41 3.1 (treatment periods I and II): safety set and safety-treatment period II subset

Treatment Period I		**CT-P41 (N=239)**	**US-Prolia (N=238)**
Number (%) of patients with dermatologic reactions		13 (5.4)	10 (4.2)
Related		1 (0.4)	1 (0.4)
Grade 1		0	1 (0.4)
Grade 2		1 (0.4)	0
Unrelated		12 (5.0)	9 (3.8)
Grade 1		4 (1.7)	5 (2.1)
Grade 2		8 (3.3)	4 (1.7)
Treatment Period II	**CT-P41 Maintenance (N=220)**	**US-Prolia Maintenance (N=100)**	**Switched to CT-P41 (N=101)**
Number (%) of patients with dermatologic reactions	0	2 (2.0)	2 (2.0)
Unrelated	0	2 (2.0)	2 (2.0)
Grade 1	0	1 (1.0)	1 (1.0)
Grade 2	0	1 (1.0)	1 (1.0)

Note: At each level of summarisation, patients are counted once if they reported one or more events. Only the most severe event was counted. The event was considered related if the relationship was defined as 'Possible', 'Probable' and 'Definite'.

2.5.8.3. Serious adverse event/deaths/other significant events

Deaths

Two deaths were reported amongst PMO patients from Study CT-P41 3.1, both in the CT-P41 group. One death was due to coronary heart disease. For the other one, cause of death was unknown, but the patient suffered from Grade 5 female malignant genital neoplasm. Both cases were considered by the investigator unrelated to study drug.

Treatment-emergent serious adverse events

Overall, 35 TESAEs were reported in 27 (5.7%) patients (14 [5.9%] and 13 [5.5%] patients in the CT-P41 and US-licensed Prolia groups, respectively; and 12 [5.5%], 8 [8.0%], and 2 [2.0%] patients in the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups, respectively). All TESAEs were considered to be unrelated to the study drug by the investigator. The majority of TESAEs were Grade 3 in severity (14 [2.9%] in total). A total of 3 (0.6%) and 2 (0.4%) patients reported TESAEs of Grade 4 and 5 in severity, respectively.

All TESAEs for the overall study period are summarised by SOC and PT in Table 35.

No TESAEs were reported in healthy male subjects in studies CT-P41 1.1 and CT-P41 1.2.

Table 35. Treatment-emergent serious adverse events by SOC and PT, Study CT-P41 3.1 (overall period): safety set and safety-treatment period II subset

System Organ Class Preferred Term	CT-P41 (N=239)	US-licensed Prolia (N=238)	CT-P41 Maintenance (N=220)	US-licensed Prolia Maintenance (N=100)	Switched to CT-P41 (N=101)	Total (N=477)
	Number (%) of patients					
Total number of TESAEs	**17**	**18**	**14**	**10**	**5**	**35**
Number of patients with at least 1 TESAE	**14 (5.9%)**	**13 (5.5%)**	**12 (5.5%)**	**8 (8.0%)**	**2 (2.0%)**	**27 (5.7%)**
Cardiac disorders	**4 (1.7%)**	**1 (0.4%)**	**3 (1.4%)**	**0**	**0**	**5 (1.0%)**
Acute myocardial infarction – grade 3	1 (0.4%)	1 (0.4%)	1 (0.5%)	0	0	2 (0.4%)
Angina unstable – grade 3, 4	2 (0.8%)	0	2 (0.9%)	0	0	2 (0.4%)
Atrial fibrillation – grade 3	1 (0.4%)	0	1 (0.5%)	0	0	1 (0.2%)
Coronary artery disease – grade 5	1 (0.4%)	0	0	0	0	1 (0.2%)
Eye disorders	**0**	**1 (0.4%)**	**0**	**1 (1.0%)**	**0**	**1 (0.2%)**
Cataract – grade 3	0	1 (0.4%)	0	1 (1.0%)	0	1 (0.2%)
Gastrointestinal disorders	2 (0.8%)	2 (0.8%)	1 (0.5%)	1 (1.0%)	1 (1.0%)	4 (0.8%)
Crohn's disease – grade 1	1 (0.4%)	0	0	0	0	1 (0.2%)
Diverticulum intestinal – grade 2	0	1 (0.4%)	0	0	1 (1.0%)	1 (0.2%)
Gastric disorder – grade 2	0	1 (0.4%)	0	0	1 (1.0%)	1 (0.2%)
Gastritis – grade 2	0	1 (0.4%)	0	1 (1.0%)	0	1 (0.2%)
Gastrointestinal perforation – grade 4	1 (0.4%)	0	1 (0.5%)	0	0	1 (0.2%)
Large intestinal stenosis – grade 2	0	1 (0.4%)	0	0	1 (1.0%)	1 (0.2%)
Infections and infestations	**0**	**1 (0.4%)**	**0**	**1 (1.0%)**	**0**	**1 (0.2%)**
COVID-19 – grade 3	0	1 (0.4%)	0	1 (1.0%)	0	1 (0.2%)
Injury, poisoning and procedural complications	**0**	**2 (0.8%)**	**0**	**1 (1.0%)**	**1 (1.0%)**	**2 (0.4%)**

Humerus fracture – grade 3	0	1 (0.4%)	0	1 (1.0%)	0	1 (0.2%)
Ligament sprain – grade 1	0	1 (0.4%)	0	0	1 (1.0%)	1 (0.2%)
Investigations	**0**	**1 (0.4%)**	**0**	**1 (1.0%)**	**0**	**1 (0.2%)**
Hormone level abnormal – grade 3	0	1 (0.4%)	0	1 (1.0%)	0	1 (0.2%)
Musculoskeletal and connective tissue disorders	**2 (0.8%)**	**1 (0.4%)**	**2 (0.9%)**	**1 (1.0%)**	**0**	**3 (0.6%)**
Arthritis – grade 2	1 (0.4%)	0	1 (0.5%)	0	0	1 (0.2%)
Osteoarthritis – grade 3	1 (0.4%)	0	1 (0.5%)	0	0	1 (0.2%)
Pain in extremity – grade 3	0	1 (0.4%)	0	1 (1.0%)	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5 (2.1%)**	**3 (1.3%)**	**4 (1.8%)**	**1 (1.0%)**	**0**	**8 (1.7%)**
Basal cell carcinoma – grade 3	0	1 (0.4%)	0	0	0	1 (0.2%)
Benign neoplasm of adrenal gland – grade 3	0	1 (0.4%)	0	1 (1.0%)	0	1 (0.2%)
Borderline ovarian tumour – grade 3	0	1 (0.4%)	0	0	0	1 (0.2%)
Breast cancer – grade 2	1 (0.4%)	0	1 (0.5%)	0	0	1 (0.2%)
Genital neoplasm malignant female – grade 5	1 (0.4%)	0	1 (0.5%)	0	0	1 (0.2%)
Invasive breast carcinoma – grade 3	1 (0.4%)	0	1 (0.5%)	0	0	1 (0.2%)
Pancreatic carcinoma – grade 2	1 (0.4%)	0	0	0	0	1 (0.2%)
Squamous cell carcinoma – grade 3	1 (0.4%)	0	1 (0.5%)	0	0	1 (0.2%)
Nervous system disorders	**0**	**1 (0.4%)**	**0**	**0**	**1 (1.0%)**	**1 (0.2%)**
Ischaemic stroke – grade 4	0	1 (0.4%)	0	0	1 (1.0%)	1 (0.2%)
Reproductive system and breast disorders	**2 (0.8%)**	**0**	**2 (0.9%)**	**0**	**0**	**2 (0.4%)**
Uterine polyp – grade 2	1 (0.4%)	0	1 (0.5%)	0	0	1 (0.2%)
Vulval leucoplakia – grade 3	1 (0.4%)	0	1 (0.5%)	0	0	1 (0.2%)

Respiratory, thoracic and mediastinal disorders	**0**	**2 (0.8%)**	**0**	**2 (2.0%)**	**0**	**2 (0.4%)**
Asthma – grade 3	0	1 (0.4%)	0	1 (1.0%)	0	1 (0.2%)
Epistaxis – grade 2	0	1 (0.4%)	0	1 (1.0%)	0	1 (0.2%)
Vascular disorders	**1 (0.4%)**	**0**	**1 (0.5%)**	**0**	**0**	**1 (0.2%)**
Peripheral arterial occlusive disease – grade 2	1 (0.4%)	0	1 (0.5%)	0	0	1 (0.2%)

Abbreviations: TESAE, treatment-emergent serious adverse event; US, United States.
Note: At each level of summarisation, a patient was counted once if the patient reported one or more events. Only the most severe event was counted. The severity was defined as Grade 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life-threatening, 5 = Death. System organ classes and preferred terms were coded using Medical Dictionary for Regulatory Activities, Version 26.0.

2.5.8.1. Laboratory findings

Healthy male subjects

Study CT-P41 1.1

The majority of laboratory parameters had no CTCAE grade or were grade 1 (mild) or grade 2 (moderate) for each laboratory parameter. There were no laboratory findings that the investigator found to be clinically significant and reported as TEAE, except 1 case of hypocalcaemia.

CTCAE grade 3 (severe) laboratory parameters were reported in 2 subjects (2/238 [13.3%] subjects in the EU-approved Prolia treatment group): one event of hypertriglyceridaemia and one event of CPK increased.

CTCAE grade 4 (life-threatening) laboratory parameters were reported in 2 subjects (2/239 [13.3 %] subjects in the CT-P41 treatment group), both events CPK increased.

There were no apparent treatment-related trends in clinical laboratory results, vital sign measurements, ECG results, or physical examination findings. Overall, mean pain score (range 0 to 100 mm on the Visual Analogue Scale) for all subjects was very low (1.9 mm for subjects in the CT-P41 treatment group and 2.0 mm in the EU-approved Prolia treatment group).

Study CT-P41 1.2

The majority of laboratory parameters had no CTCAE grade or were grade 1 (mild) or grade 2 (moderate). The most frequently reported CTCAE grade 1 or grade 2 laboratory parameters were hypertriglyceridemia, followed by high cholesterol. In general, there was no notable difference between the 2 treatment groups.

Table 36. Most severe CTCAE grading of laboratory parameters (CTCAE grade 3 or higher): safety set. Study CT-P41 1.2

CTCAE Term CTCAE Grade	**CT-P41 (N=74)**	**US-Prolia (N=77)**
Clinical Chemistry		
CPK increased		
Grade 3	3 (4.1)	2 (2.6)
Grade 4	2 (2.7)	0
Cholesterol high		
Grade 3	0	1 (1.3)
Hypermagnesemia		
Grade 3	2 (2.7)	2 (2.6)
Hypertriglyceridemia		
Grade 3	6 (8.1)	5 (6.5)
Grade 4	3 (4.1)	1 (1.3)
Haematology		
Neutrophil count decreased		
Grade 3	1 (1.4)	0

Note: A subject was counted once using the most severe grade across all post-baseline visits.
Abbreviations: CPK, creatine phosphokinase; CTCAE, common terminology criteria for adverse events

Patients with postmenopausal osteoporosis

Study CT-P41 3.1

The majority of laboratory parameters had no CTCAE grade (e.g., the post-baseline laboratory result did not satisfy any CTCAE grade criteria) or were CTCAE Grade 1 (mild) or Grade 2 (moderate). In general, there was no notable difference among all groups for patients with any Grade of CTCAE in laboratory parameters.

Post-baseline CTCAE Grade 3 or higher laboratory results for the Overall period of Study CT-P41 3.1 are summarised in Table 37. The most frequently reported CTCAE Grade 3 or higher laboratory parameter as worst value during Overall Period was Grade 3 neutrophil count decreased which was reported for 7 (1.5%) patients (2 [0.8%] and 5 [2.1%] patients in the CT-P41 and US-licensed Prolia groups, respectively; and 2 [0.9%], 2 [2.0%], and 2 [2.0%] patients in the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups, respectively) and no Grade 4 laboratory parameter as worst value was reported in any of the treatment groups.

The second most commonly reported CTCAE Grade 3 or higher laboratory parameters was Grade 3 CPK increased which was reported for 3 (0.6%) patients (1 [0.4%] and 2 [0.8%] patients in the CT-P41 and US-licensed Prolia groups, respectively; and 1 [0.5%], 1 [1.0%], and 1 [1.0%] patients in the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups, respectively). Similarly, no Grade 4 laboratory parameter as worst value was reported in any of the treatment groups.

Table 37. Post-baseline CTCAE grade 3 or higher laboratory results in study CT-P41 3.1 (overall period): safety set

CTCAE Term Grade	CT-P41 (N=239)	US-licensed Prolia (N=238)	CT-P41 Maintenance (N=220)	US-licensed Prolia Maintenance (N=100)	Switched to CT-P41 (N=101)	Total (N=477)
	Number (%) of patients					
Clinical Chemistry						
Alanine aminotransferase increased						
Grade 3 (Severe)	1 (0.4%)	1 (0.4%)	1 (0.5%)	0	1 (1.0%)	2 (0.4%)
CPK increased						
Grade 3 (Severe)	1 (0.4%)	2 (0.8%)	1 (0.5%)	1 (1.0%)	1 (1.0%)	3 (0.6%)
Hypercalcemia						
Grade 3 (Severe)	1 (0.4%)	0	1 (0.5%)	0	0	1 (0.2%)
Hypertriglyceridemia						
Grade 3 (Severe)	2 (0.8%)	0	2 (0.9%)	0	0	2 (0.4%)
Haematology						
Lymphocyte count decreased						
Grade 3 (Severe)	0	1 (0.4%)	0	0	0	1 (0.2%)
Neutrophil count decreased						
Grade 3 (Severe)	2 (0.8%)	5 (2.1%)	2 (0.9%)	2 (2.0%)	2 (2.0%)	7 (1.5%)

Abbreviations: CPK, creatine phosphokinase; CTCAE, common terminology criteria for adverse events; US, United States. Note: All results including unscheduled visits collected after the first study drug administration were used.

2.5.8.2. Safety in special populations

Not applicable for biosimilars.

2.5.8.3. Immunological events

Bioanalytical methods for determination of anti-drug antibodies (ADA) and neutralising antibodies (NAb) are assessed in Section 2.5.2 of this AR.

Immunogenicity in studies CT-P41 1.1 and 1.2 conducted in healthy male subjects is assessed in Section 2.5.2 of this AR. Immunogenicity results of these Phase 1 studies were concordant with those observed in the Phase 3 study CT-P41 3.1 (see below), showing similar immunogenicity profile of CT-P41 with that of EU-Prolia and US-Prolia.

In Study CT-P41 3.1, samples for ADA and NAb were drawn at Day 1 and Weeks 2, 4, 8, 12, 26, 39, 52, 60, 68 and 78 (end of study, EOS). Samples were drawn prior to study drug administration, when study drug was administered on the same visit (Day 1, Week 26 and Week 52). Additional immunogenicity was to be assessed when suspected immune-related AEs occurred.

The immunogenicity profile was overall comparable between the CT-P41 and US-Prolia groups during Treatment Period I and between CT-P41 Maintenance, US-Prolia, and Switched to CT-P41 groups during Treatment Period II (Table 38 and Table 39).

The majority of the patients turned ADA positive during the study. The highest ADA positive rates were observed at Week 12 and were 84.1% (201/239) and 86.6% (206/238) in the CT-P41 and US-licensed Prolia groups, respectively. The proportion of ADA positive subjects fluctuated during the study, increasing in visits following study drug administration and decreasing already prior to next study drug administration. The proportion of patients that were ADA positive at least once after the first study drug administration was similar between the 2 groups (233/239 [97.5%] patients and 234/238 [98.3%] patients in the CT-P41 and US-licensed Prolia groups, respectively).

None of the patients were NAb positive at any time point of the study.

Table 38. Summary of immunogenicity (ADA and NAb) results (treatment period I): safety set

Visit ADA Result NAb Result	CT-P41 (N=239) Number (%) of Patients	US-licensed Prolia (N=238)	Total (N=477)
Patients with at least 1 result after the first study drug administration of			
Treatment Period I			
Positive	233 (97.5%)	234 (98.3%)	467 (97.9%)
Positive[1]	0	0	0
Week 0 (Day 1)			
Positive	2 (0.8%)	0	2 (0.4%)
Positive	0	0	0
Negative	2 (0.8%)	0	2 (0.4%)
Negative	237 (99.2%)	238 (100.0%)	475 (99.6%)
Week 2			
Positive	71 (29.7%)	90 (37.8%)	161 (33.8%)
Positive	0	0	0
Negative	71 (29.7%)	90 (37.8%)	161 (33.8%)
Negative	153 (64.0%)	134 (56.3%)	287 (60.2%)
Week 4			
Positive	156 (65.3%)	163 (68.5%)	319 (66.9%)
Positive	0	0	0
Negative	156 (65.3%)	163 (68.5%)	319 (66.9%)
Negative	75 (31.4%)	70 (29.4%)	145 (30.4%)
Week 8			
Positive	195 (81.6%)	194 (81.5%)	389 (81.6%)
Positive	0	0	0
Negative	195 (81.6%)	194 (81.5%)	389 (81.6%)
Negative	39 (16.3%)	37 (15.5%)	76 (15.9%)
Week 12			
Positive	201 (84.1%)	206 (86.6%)	407 (85.3%)
Positive	0	0	0
Negative	201 (84.1%)	206 (86.6%)	407 (85.3%)
Negative	33 (13.8%)	26 (10.9%)	59 (12.4%)
Week 26			
Positive	58 (24.3%)	66 (27.7%)	124 (26.0%)
Positive	0	0	0
Negative	58 (24.3%)	66 (27.7%)	124 (26.0%)
Negative	169 (70.7%)	155 (65.1%)	324 (67.9%)
Week 39			
Positive	197 (82.4%)	189 (79.4%)	386 (80.9%)
Positive	0	0	0
Negative	197 (82.4%)	189 (79.4%)	386 (80.9%)
Negative	26 (10.9%)	19 (8.0%)	45 (9.4%)
Week 52			
Positive	81 (33.9%)	79 (33.2%)	160 (33.5%)
Positive	0	0	0
Negative	81 (33.9%)	79 (33.2%)	160 (33.5%)
Negative	140 (58.6%)	128 (53.8%)	268 (56.2%)

Abbreviations: ADA, anti-drug antibody, NAb, neutralizing antibody.
Note: The ADA test involved both screening and confirmatory assay to confirm positive results. Samples that were 'potential positive' in the screening assay were further tested in the confirmatory assay to ensure that the patients were a true positive labelled 'positive'. Only patients with a positive ADA result were included in the NAb summary.
1. The denominator was the number of patients who had at least 1 ADA positive results. Source:

Table 39. Summary of immunogenicity (ADA and NAb) results (treatment period ii): safety-treatment period II subset

Visit ADA Result NAb Result	CT-P41 Maintenance (N=220)	US-licensed Prolia Maintenance (N=100)	Switched to CT-P41 (N=101)	Total (N=421)
	Number (%) of Patients			
Patients with at least 1 result after the first study drug administration of Treatment Period II				
Positive	208 (94.5%)	92 (92.0%)	93 (92.1%)	393 (93.3%)
Positive[1]	0	0	0	0
Week 60				
Positive	189 (85.9%)	88 (88.0%)	89 (88.1%)	366 (86.9%)
Positive	0	0	0	0
Negative	189 (85.9%)	88 (88.0%)	89 (88.1%)	366 (86.9%)
Negative	28 (12.7%)	7 (7.0%)	10 (9.9%)	45 (10.7%)
Week 68				
Positive	168 (76.4%)	75 (75.0%)	82 (81.2%)	325 (77.2%)
Positive	0	0	0	0
Negative	168 (76.4%)	75 (75.0%)	82 (81.2%)	325 (77.2%)
Negative	47 (21.4%)	21 (21.0%)	18 (17.8%)	86 (20.4%)
Week 78				
Positive	74 (33.6%)	35 (35.0%)	39 (38.6%)	148 (35.2%)
Positive	0	0	0	0
Negative	74 (33.6%)	35 (35.0%)	39 (38.6%)	148 (35.2%)
Negative	140 (63.6%)	62 (62.0%)	59 (58.4%)	261 (62.0%)

Abbreviations: ADA, anti-drug antibody, NAb, neutralizing antibody.
Note: The ADA test involved both screening and confirmatory assay to confirm positive results. Samples that were 'potential positive' in the screening assay were further tested in the confirmatory assay to ensure that the patients were a true positive labelled 'positive'. Only patients with a positive ADA result were included in the NAb summary.
1. The denominator was the number of patients who had at least 1 ADA positive results.

ADA titres were mostly low and similar across study groups, with median values in the range of 100 to 300.

No impact of ADA positivity or titre on PK, PD, BMD outcome or safety was observed in post hoc analyses conducted by the applicant.

2.5.8.4. Safety related to drug-drug interactions and other interactions

Not applicable for biosimilars.

2.5.8.5. Discontinuation due to adverse events

For Study CT-P41 1.2 and Study CT-P41 1.1, there were no deaths, TESAEs or TEAEs leading to study discontinuation.

In patients with postmenopausal osteoporosis in Study CT-P41 3.1, TEAEs leading to discontinuation of study drug occurred during TP I in 5/239 (2.1%) and 5/238 (2.1%) patients in the CT-P41 and US-licensed Prolia groups, respectively. The reasons for discontinuation during TP1 are summarised in Table 40. Apart from the case of osteonecrosis of jaw, all the events leading to discontinuation were considered unrelated to study drug.

There were no discontinuations of study drug due to TEAEs during TP II.

Table 40. TEAEs leading to study drug discontinuation by SOC and PT in study CT-P41 3.1 (treatment period I): safety set

System Organ Class Preferred Term	CT-P41 (N=239)	US-licensed Prolia (N=238)	Total (N=477)
	Number (%) of patients		
Total number of TEAEs leading to discontinuation of study drug	**5**	**6**	**11**
Number of patients with at least 1 TEAE	**5 (2.1%)**	**5 (2.1%)**	**10 (2.1%)**
Related to the study drug	0	2 (0.8%)	2 (0.4%)
Unrelated to the study drug	5 (2.1%)	3 (1.3%)	8 (1.7%)
Eye disorders	**0**	**1 (0.4%)**	**1 (0.2%)**
Cataract – grade 2	0	1 (0.4%)	1 (0.2%)
Gastrointestinal disorders	**2 (0.8%)**	**0**	**2 (0.4%)**
Crohn's disease – grade 1	1 (0.4%)	0	1 (0.2%)
Toothache – grade 2	1 (0.4%)	0	1 (0.2%)
Infections and infestations	**1 (0.4%)**	**0**	**1 (0.2%)**
Respiratory tract infection – grade 2	1 (0.4%)	0	1 (0.2%)
Investigations	**1 (0.4%)**	**1 (0.4%)**	**2 (0.4%)**
Alanine aminotransferase increased – grade 2	0	1 (0.4%)	1 (0.2%)
Hepatic enzyme increased – grade 2	1 (0.4%)	0	1 (0.2%)
Musculoskeletal and connective tissue disorders	**0**	**1 (0.4%)**	**1 (0.2%)**
Osteonecrosis of jaw – grade 2	0	1 (0.4%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.4%)**	**2 (0.8%)**	**3 (0.6%)**
Basal cell carcinoma – grade 3	0	1 (0.4%)	1 (0.2%)
Borderline ovarian tumour – grade 3	0	1 (0.4%)	1 (0.2%)
Pancreatic carcinoma – grade 2	1 (0.4%)	0	1 (0.2%)

Abbreviations: TEAE, treatment-emergent adverse event; US, United States.

Note: At each level of summarisation, a patient was counted once if the patient reported one or more events. Only the most severe event was counted. The event was considered to be related if the relationship is defined as 'Possible', 'Probable' and 'Definite'. The severity is defined as Grade 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life-threatening, 5 = Death. System organ classes and preferred terms were coded using Medical Dictionary for Regulatory Activities, Version 26.0.

2.5.8.6. Post marketing experience

Not applicable

2.5.9. Discussion on clinical safety

The safety information is based on data from Study CT-P41 3.1 in PMO patients and from Study CT-P41 1.1 and Study CT-P41 1.2 in healthy male subjects.

Study CT-P41 1.1 (pilot study) is completed with safety data up to Day 134 with a total of 30 subjects (15 subjects in the CT-P41 group and 15 subjects in the EU-Prolia group). Study CT-P41 1.2 is

completed with safety data up to Day 253 with a total of 151 subjects (74 subjects in the CT-P41 group and 77 subjects in the US-Prolia group).

Safety set for Treatment Period I of Study CT-P41 3.1, which compares CT-P41 and US-Prolia in the treatment of osteoporosis, includes 477 patients (239 and 238 patients in the CT-P41 and US-licensed Prolia groups, respectively). The Safety-Treatment Period II Subset included 421 patients (220 patients, 100 patients, and 101 patients in the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups, respectively). The final CSR for this study was received with the response to D120 LoQ. Data are provided by separate study periods (Treatment Period I and Treatment Period II) and Overall Period, which includes all study periods, throughout the sections.

The safety data for comparison between CT-P41 and EU-Prolia includes only study CT-P41 1.1, a single dose study conducted in healthy men. This number would alone be too low for confirmation of comparable safety; especially as the study only contained one single dose. Similarly, no clinical studies were conducted with Xgeva as comparator. Nevertheless, analytical similarity of CT-P41 has been demonstrated in a 3-way analytical similarity assessment using EU-authorised as well as US-licensed Prolia and Xgeva. Therefore, the results obtained in studies with US-Prolia as comparator can be extrapolated to EU-Prolia and Xgeva.

In the pilot study CT-P41 1.1 (n=30), TEAEs were reported for 6/15 (40.0%) and 12/15 (80.0%) subjects in the CT-P41 and EU-Prolia groups, respectively. Of these, TEAEs related to the study drug by the investigator were reported in 3/15 subjects (20.0%) in the CT-P41 treatment group and 6/15 subjects (40.0%) in the EU-approved Prolia treatment group. The different (more favourable) safety profile of CT-P41 vs. EU-Prolia in the small pilot study is likely to be due to chance, taking in account the similar safety profile of CT-P41 and US-Prolia in healthy male subjects in Study CT-P41 1.2 (N=151, CT-P41 n=74, US-Prolia n=77).

In study CT-P41 1.2, 282 TEAEs were reported from 114/151 (75.5%) subjects, of which 55/74 (74.3%) and 59/77 (76.6%) of subjects in the CT-P41 and US-Prolia treatment groups, respectively. TEAEs considered to be related to study drug were reported in 39/74 (52.7%) and 45/77 (58.4%) subjects in the CT-P41 and US-Prolia groups, respectively. In Study CT-P41 1.2 and Study CT-P41 1.1, there were no deaths, TESAEs or TEAEs leading to study discontinuation.

In Study CT-P41 3.1, the overall safety profile was consistent with the known safety profile of Prolia. There were no new or unexpected safety findings and the majority of TEAEs were Grade 1 or 2 in severity. The distribution of patients was comparable across all SOCs except for infections and infestations, the rate of which was reported comparably higher in patients who received CT-P41 in both treatment periods. During the overall period, TEAEs of infections were reported for 111/239 (46.4%) patients in the CT-P41 group, 90/238 (37.8%) patients in the US-Prolia group, 102/220 (46.4%) in the CT-P41 Maintenance group, 36/100 (36.0%) patients in the US-Prolia Maintenance group and 47/101 (46.5%) patients in the Switched to CT-P41 group. E.g., upper respiratory tract infections (URTI) and urinary tract infections (UTI) were more common during treatment with CT-P41. These events are a known risk that is included in Section 4.8 of the Prolia SmPC as common AEs. The overall severity of infection related TEAEs was either Grade 1 or 2 and only 6 cases were assessed as related to the study drug out of 338 TEAEs classified as infections.

Upon request, the applicant analysed further the reported infections and opportunistic infections. No clear reason for the observed differences between study arms in incidence of infections was identified; except that according to post-hoc analyses, there appears to have been, among the subjects who reported infections, more high-risk subjects susceptible to infections in the CT-P41 group. The observed difference in incidence of URTI and UTI in the CT-P41, CT-P41 Maintenance and Switched to CT-P41 groups vs. the US-Prolia and US-Prolia Maintenance groups contributed to the overall difference in reported infections. A total of 13 events (about 3.8% of all infection events) were

categorised as opportunistic infections and included herpes zoster, respiratory syncytial virus infection, pneumonia, vulvovaginal mycotic infection, and staphylococcal skin infection. There were no cases of TB reported in the study. All OIs were non-serious and either Grade 1 or 2 in severity. Overall, the incidence of OIs was low and no significant safety issue was found.

Taking in account the similar PK, PD and efficacy profile of CT-P41 and US-Prolia, the observed small differences in infection rate between study groups are likely due to chance.

The noted infections do not warrant an update of the Product Information, since no new infection AEs were identified.

The most commonly reported AEs considered related to study drug were parathyroid hormone (PTH) increase and injection site reactions (ISR), most commonly injection site erythema. Incidence of the TEAE 'PTH increased' was balanced across study groups: 5 (2.1%) and 9 (3.8%) patients in the CT-P41 and US-licensed Prolia groups, respectively; and 5 (2.3%), 6 (6.0%), and 2 (2.0%) patients in the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups, respectively). The increase in PTH is not listed in Section 4.8 of the SmPC, but hypocalcaemia is a known risk and often preceded by reactive increase in PTH already prior to the decrease in the calcium level. There were numerically more ISR in subjects administered CT-P41, but overall, in a small number of subjects. During the Overall Period, TEAEs of ISR were reported for 8 (3.3%) patients in the CT-P41 group, 4 (1.7%) patients in the US-Prolia group, 8/220 (3.6%) in the CT-P41 Maintenance group, no patients in the US-Prolia Maintenance group and 2 (2.0%) patients in the Switched to CT-P41 group.

No marked differences in incidence were observed in other AEs of special interest than infections in study CT-P41 3.1. In the studies with healthy males also rates of infection were comparable.

The proportion of subjects discontinuing study drug due to TEAEs was low and similar with CT-P41 and US-Prolia in patients with postmenopausal osteoporosis: 2,1% in each group during TP 1 and none during TP2 of study CT-P41 3.1. Apart from one case of osteonecrosis of jaw (in the US-Prolia group), TEAEs leading to discontinuation were considered unrelated to study drug.

No discontinuation due to TEAE was observed in healthy male subjects.

The immunogenicity results of all clinical studies showed that a great majority of patients reported at least 1 positive ADA result after the first study drug administration. In Study CT-P41 3.1 in PMO patients, 233/293 (97.5%) and 234/238 (98.3%) of patients in the CT-P41 and US-licensed Prolia groups, respectively, had at least one positive ADA result during the study. ADA-positivity fluctuated in all study groups, with increases after each dose and decreases thereafter up to next dose. In this study, none of patients had positive NAb results.

In healthy male subjects in Study CT-P41 1.1, one (1/15) subject (6.7%) in the CT-P41 treatment group and none in the EU-Prolia group had a positive NAb result on Day 85; and this subject was NAb negative again at EOS visit. In Study CT-P41 1.2, 2.7% (2/74) subjects in the CT-P41 group and 2.6% (2/77) subjects in the US-Prolia group had at least one ADA/NAb positive result during the study. The ADA titre values at the time of NAb positive result were all low at 100. All of these 4 subjects were ADA negative on Day 253 (EOS).

The incidence of ADA in all clinical studies for CT-P41 was markedly higher than in the studies for MAA of Prolia. However, in all studies, the ADA incidence between CT-P41 and US/EU-Prolia was comparable. The observed incidence of a positive antibody test result may be influenced by several factors, including assay methodology and sample properties; hence, comparison to historical studies is not deemed relevant.

Post-hoc analyses showed no impact of presence or titre of ADAs on efficacy, safety, PK or PD.

2.5.10. Conclusions on the clinical safety

Overall, the safety profile of CT-P41 appears to be similar to that of US-Prolia. Obtained data with US-Prolia as comparator can be extrapolated to similar clinical effects of CT-P41 compared with EU-Prolia and with Xgeva, since analytical similarity of CT-P41 has been demonstrated in a 3-way analytical similarity assessment using EU-authorised as well as US-licensed Prolia and Xgeva.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 41. 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	• Patients with prior intravenous bisphosphonate treatment • 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 42. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Osteonecrosis of the jaw (Important identified risk)	Routine risk minimisation measures: • *SmPC sections 4.3, 4.8 and 5.1* • *SmPC section 4.4 where maintenance of oral hygiene, regular dental management and potential oral symptoms of ONJ are included* • *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Atypical fracture femoral (Important identified risk)	Routine risk minimisation measures: • *SmPC section 4.8* • *SmPC section 4.4 where recommendations for monitoring patients for signs and symptoms of hypercalcaemia after discontinuation of treatment are included* • *PL section 2 where recommendations for reporting new or unusual pain in hip, groin, or thigh are included* • *PL section 4 where possible signs of thigh bone fracture are included* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons (Important identified risk)	Routine risk minimisation measures: • *SmPC section 4.8* • *SmPC section 4.4, where recommendations for signs and symptoms of hypercalcaemia after discontinuation of treatment are included* • *PL section 4* • *PL section 2, where recommendations for monitoring signs and symptoms of high levels of calcium after stopping treatment are included* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Cardiovascular events (Important potential risk)	Routine risk minimisation measures: *None* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Malignancy (Important potential risk)	Routine risk minimisation measures: • *SmPC sections 4.8 and 5.1* • *SmPC section 4.4, where recommendations for monitoring patients for radiological signs of malignancy, new radiolucency or osteolysis are included* • *PL section 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Delay in diagnosis of primary malignancy in giant cell tumour of bone (Important potential risk)	Routine risk minimisation measures: None Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons (Important potential risk)	Routine risk minimisation measures: None Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with previous intravenous treatment with bisphosphonate treatment (Missing information)	Routine risk minimisation measures: • *SmPC sections 4.5 and 5.1* • *PL section 2* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
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 (Missing information)	Routine risk minimisation measures: None Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity (Missing information)	Routine risk minimisation measures: None Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse 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.

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 Xgeva(EMEA/H/C/002173) and Herzuma (EMEA/H/C/002575). The bridging report submitted by the applicant has been found acceptable.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Osenvelt was developed as a biosimilar against EU-XGEVA (INN: denosumab) having same strength and presentation, 120 mg solution for injection in vial. Innovator is on market by Amgen.

EU-XGEVA has following indications:

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

In the current MAA, the applicant seeks the same indications as approved for EU-XGEVA.

Summary of quality data

The applicant is developing two biosimilars; CT-P41 60mg PFS (Stoboclo) for reference product Prolia and CT-P41 120 mg vial (Osenvelt) for reference product Xgeva. Analytical similarity study was performed. The similarity assessment study of CT-P41 vial, EU-Xgeva, and US Xgeva was designed to confirm the results of analytical similarity studies of EU-/US-Prolia and CT-P41 60 mg PFS FP. Received CHMP scientific advice has been followed in the presented similarity exercise.

CT-P41 60mg PFS and EU-Prolia are identical with respect to pharmaceutical form, concentration, and route of administration. CT-P41 120mg vial and EU-Xgeva are identical with respect to pharmaceutical form, concentration, and route of administration. The composition of CT-P41 is identical to that of EU-/US-Prolia (PFS) but slightly different from that of EU-/US-Xgeva (vial) in excipients.

The 3-way analytical similarity assessment also serves as a bridging study between EU-Prolia and US-Prolia and between EU-Xgeva and US-Xgeva. The clinical trials CT-P41 1.2 and CT-P41 3.1 have been made with US-Prolia and clinical trial CT-P41 1.1 with EU-Prolia.

The applicant provided sufficient raw data of the individual analytical results allowing assessment of biosimilarity independently of the chosen statistical approach and the provided data is considered appropriate to define conclusions on analytical similarity.

The analytical similarity assessments included a similarity analysis of primary and higher order structure, purity/impurity, content, glycan profiles and post-translational modifications, as well as biological assays. All methods used in the similarity assessment were appropriately qualified or validated to confirm suitability of use.

Summary of Non-clinical data

The non-clinical comparative assessment included a battery of *in vitro* functional activity studies which are presented under the Quality data. In addition, a GLP-compliant 4-week repeat-dose toxicology and toxicokinetics study was conducted in cynomolgus monkeys.

Summary of Clinical data

CT-P41 is a biosimilar product for Amgen denosumab, intended to be marketed with two different brand names, Stoboclo and Osenvelt, similarly to innovator (EU-Prolia, EU-XGEVA) containing the same active substance, but with separate indications, strengths and presentations. In the current clinical development, the applicant has used only EU- and US-licenced Prolia as a control treatment.

The program to demonstrate clinical similarity contained 3 different studies, two Phase 1 PK/PD studies and one confirmatory Phase 3 efficacy, safety, and immunogenicity study.

Study CT-P41 1.1 was a pilot phase 1, randomised, double-blind, two-arm, parallel group, single-dose study, which was designed to evaluate the safety, immunogenicity, PK/PD of CT-P41 and EU-approved Prolia in healthy male subjects. Overall, 32 subjects were randomised in a 1:1 ratio to receive a single dose (60 mg) of CT-P41 or EU-approved Prolia.

Study CT-P41 1.2 was a phase 1, randomised, double-blind, two-arm, parallel group, single-dose study to compare PK/PD, safety and immunogenicity between CT-P41 and US-licensed Prolia in 154 healthy

male subjects randomised 1:1 (76 subjects in CT-P41 group and 78 in US-Prolia group). The primary PK endpoints were $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max} . PK sampling was conducted on day 1 (pre-dose, 6 h and 12 h post-dose), 2, 3, 4, 6, 8, 11, 15, 22, 29, 43, 57, 71, 85, 99, 113, 141, 169, 197, and 253 and in case of early termination. PD sampling was conducted on day 1 (pre-dose), 2, 3, 4, 8, 15, 29, 85, 141, 197 and 253 and in case of early termination.

Study CT-P41 3.1 was a randomised, double-blind, active-controlled, parallel group, Phase 3 study to compare the efficacy, PK, PD, immunogenicity and overall safety of CT-P41 and US-Prolia in 477 postmenopausal women with osteoporosis randomised 1:1 (239 subjects in CT-P41 group and 238 in US-Prolia group). The study was carried out in 20 study centres in 4 countries (Latvia, Poland, Ukraine, Estonia). After the screening period (4 weeks), the study subjects were randomised 1:1 to receive two 60 mg s.c. doses of CT-P41 or US-Prolia with 6-month period in between doses. At Week 52 (second randomisation) half of the patients in US-Prolia group were re-randomised in blind to switch to receive CT-P41 and half of the control group subjects continued with their initially allocated treatment. All patients in the CT-P41 group continued to treatment period II. The full length of study (treatment and follow up period) was 78 weeks. Overall, the study was according to the three CHMP scientific advises received (EMEA/H/SA/4399/1/2020/III, EMEA/H/SA/4399/1/FU/1/2020/II, EMA/SA/0000050271), and acceptable.

3.2. Results supporting biosimilarity

Quality

Similarity between CT-P41 and EU-Xgeva has been demonstrated for the following physicochemical and biological properties:

- Primary structure and post-translational modifications
- Charged variants
- Glycation and glycosylation
- Purity/impurity (size variants)
- Higher order structure
- Content (protein concentration)
- Comparative stability studies (forced degradation, accelerated and stressed stability)
- Biological activity
    - Fab binding related (RANKL binding, Cell-based RANKL binding, RANKL binding inhibition Assay with RANK, RANKL binding inhibition Assay with OPG, Osteoclastogenesis Inhibition Assay
    - Fc binding related (C1q, FcγRIIIb, FcγRIIa, FcγRIIb, and FcγRIa, FcRn as well as lack of ADCC and CDC activity)

Non-clinical

The supportive repeat-dose toxicity study in cynomolgus monkeys did not reveal significant differences between CT-P41 and US-Prolia in the toxicokinetic and toxicology endpoints. This data is considered as representative also for CT-P41 and EU/US-Xgeva comparison.

Clinical PK/PD

Study CT-P41 1.1

The PK/PD was as a secondary endpoint.

PK

The serum concentrations and the studied PK parameters (i.e., $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, t_{max}, $T_{1/2}$, λ_z, CL/F, Vz/F and %AUCext) were generally comparable between CT-P41 and EU-Prolia groups. Although slightly higher serum concentrations and bigger numerical values in the exposure parameters were observed in the EU-Prolia group compared to the CT-P41 group, these differences can be attributed to protein content differences in the used batches (CT-P41 batch: protein content 57.2 mg/ml and EU-Prolia batch: 59.6 mg/ml) and random variability due to small sample size.

PD

Based on the descriptive data from the CT-P41 1.1 study, the curves on median percent change from baseline for serum concentration of s-CTX as well as for P1NP following a single SC administration of CT-P41 or EU-Prolia were comparable.

Study CT-P41 1.2

PK

Biosimilarity in PK of CT-P41 and US-Prolia was shown in healthy male subjects. The point estimate of the ratio (CT-P41/US-Prolia) of the geometric mean for $AUC_{0\text{-inf}}$ was 1.07 with the corresponding 90% CI being (1.0039; 1.1465). The lower limit of 90% CI was over 1.0 and consequently, the range did not include 1.00, however, this is not any concern. The point estimate of the ratio (CT-P41/US-Prolia) of the geometric mean for $AUC_{0\text{-last}}$ was 1.07 with the 90% CI being (0.9992; 1.1428). The point estimate of the ratio (CT-P41/US-Prolia) of the geometric mean for C_{max} was 1.01 with the corresponding 90% CI being (0.9520; 1.0734). Thus, all primary PK endpoints were met as all results were within the pre-defined equivalence margin of (0.80, 1.25).

In addition, the means of the secondary PK parameters (i.e., $T_{1/2}$, $pAUC_{0\text{-w16}}$, $pAUC_{w16\text{-inf}}$, $\%AUC_{ext}$, λ_z, CL/F, Vz/F, MRT) and median t_{max} were comparable between studied treatments supporting the PK similarity.

PD

In the pivotal Phase 1 study in healthy male volunteers, the geometric LS means for the secondary PD endpoint, s-CTX AUEC over the study period, were 19086.4 and 18833.0 for the CT-P41 and US-Prolia group, respectively. The ratio of LS geometric mean of s-CTX AUEC over the study period was 101.35% with the 95% CI between 97.19% and 105.68%. The CI being entirely contained within the pre-defined equivalence limits of 80% to 125%. The 95% CI contained also value 100% meeting the criterion for the PD equivalence between the compared products.

For the secondary PD endpoint, P1NP AUEC over the study period, the geometric LS means were 11687.6 and 12520.5 for the CT-P41 and US-Prolia group, respectively. The ratio of LS geometric mean was 93.35% with the 95% CI between 83.55% and 104.29%, the margin being entirely contained within the equivalence limits of 80% to 125%. The 95% CI contained also value 100% meeting the criterion for the PD equivalence between the compared products in healthy male volunteers.

In the secondary endpoint, the median percent change from baseline of s-CTX and P1NP at each study visit, showed practically overlapping curves for the s-CTX parameter until D141 visit and throughout the whole 1-year treatment period for the P1NP parameter.

Study CT-P41 3.1

PK

Treatment period I

The mean serum concentrations from day 3 until week 52 were numerically slightly higher in the CT-P41 group than US-Prolia group, but the concentrations can be considered to be comparable between the CT-P41 and US-Prolia. The same trend could be seen in the C_{trough} concentrations at weeks 0, 26 and 52. The PK parameters AUC_{0-t}, C_{max}, T_{max}, Vd and $T_{1/2}$ were quite similar between studied treatments.

Treatment period II

The serum concentrations observed up to week 78 were generally comparable between the CT-P41, US-Prolia and "switched from US-Prolia to CT-P41" groups.

PD

In Phase 3 study CT-P41 3.1, the geometric LS means for the Phase 3 co-primary PD endpoint, s-CTX AUEC over the initial 6 months in FAS population, were 13835.4 and 14572.6 for CT-P41 and US-Prolia group, respectively. The geometric LS mean ratio was 94.94% with the 95% CI [90.75%, 99.32%] being entirely contained within the pre-defined equivalence limits of 80% to 125%.

The curves for the secondary endpoint of median percent change from baseline for serum concentration of s-CTX and P1NP throughout the whole 1-year treatment period was practically overlapping.

Efficacy

Study CT-P41 3.1

The similarity in clinical efficacy was demonstrated with a sensitive continuous primary endpoint of the %CfB in LS-BMD at Week 52 in primary FAS population. The percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52 was 4.9317 for the CT-P41 group and 5.0706 for the US-Prolia group in FAS population. The LS mean difference between the groups was -0.139 (95% CI -0.826, 0.548) being within the pre-specified equivalence range of ±1.503% with a clear margin and meeting the outcome criteria for the primary efficacy endpoint. The primary efficacy endpoint was also met in PPS population with the difference between the groups being -0.280 (95% CI -0.973, 0.414). Thus, the biosimilarity criterion for the pre-specified primary efficacy endpoint was reached. Since efficacy endpoint was a co-primary to PD endpoint s-CTX (AUEC over the initial 6 months), both should provide assurance on comparable primary clinical outcome (see discussion on PD endpoint above).

In the secondary efficacy endpoint, the mean LS-, total hip, and femoral neck BMD at week 26, 52, and 78, support to the primary endpoint outcome was reached. The level of improvement remained closely similar in all groups at the maintenance phase and no meaningful difference to switch group was present. In another secondary endpoint, the frequency of new fractures remained very low and based on the data no meaningful difference between groups can be derived. In health-related quality of life endpoints (OPAQ-SV and EQ-5D-5L), all the changes and differences between groups were minimal and have no significance on interpretation of the clinical outcome.

In summary, the descriptive secondary endpoint data do not change the overall conclusion on the similarity in efficacy between the compared treatment arms.

Safety

In the Phase 1 study CT-P41 1.2, the safety profile in healthy men was comparable between CT-P41 and US-Prolia. Overall, 282 TEAEs were reported in this study from 114 (75.5%) subjects, of which 55 (74.3%) and 59 (76.6%) of subjects in the CT-P41 and US-Prolia treatment groups, respectively. TEAEs considered to be related to study drug were reported in 39 (52.7%) and 45 (58.4%) subjects in the CT-P41 and US-Prolia groups, respectively. In Studies CT-P41 1.1 and Study CT-P41 1.2, there were no deaths, TESAEs or TEAEs leading to study discontinuation.

In Study CT-P41 3.1 in patients with postmenopausal osteoporosis, the overall safety profile was consistent with the known safety profile of Prolia. The number (%) of patients with ≥1 TEAE was 193/239 (80.8%) and 183/238 (76,9%) in the CT-P41 and US-Prolia groups, respectively. The respective number (%) of patients with ≥1 TEAE was 177/220 (80.5%) for the CT-P41 Maintenance, 75/100 (75.0%) US-Prolia Maintenance and 82/101 (81.2%) for the Switched to CT-P41 groups. There were no new or unexpected safety findings and the majority of TEAEs were Grade 1 or 2 in severity. The distribution of patients was comparable across all SOCs, except for infections and infestations, for which incidence was reported comparably higher in patients who received CT-P41 in both treatment periods.

Immunogenicity

Similar immunological profiles in healthy male subjects were seen for CT-P41 and EU-Prolia in study CT-P41 1.1 and for CT-P41 and US-Prolia in study CT-P41 1.2; and for CT-P41 and US-Prolia in patients with postmenopausal osteoporosis in Study CT-P41 3.1. Close to all subjects developed ADA during all studies. Even though ADA were detected in a high proportion of study subjects in all studies, most of the ADA titre values were low at 100 or 300 in all treatment groups in all studies. One subject in study CT-P41 1.1 (1/15 in the CT-P41 group) and none in the EU-Prolia group had an ADA/NAb positive sample; and this subject was NAb negative again at EOS visit. In study CT-P41 1.2, four (4/151) subjects had positive NAb results at least once, two (2) subjects in both treatment groups. However, all study subjects, including the 4 subjects with NAb, had turned ADA (and NAb) negative when tested on Day 253 (EOS). In Study CT-P41 3.1 in patients with postmenopausal osteoporosis no patient was NAb positive at any time point of the study.

Median ADA titres were low (in the range of from 100 to 300) in all three studies.

Post hoc analyses from Studies CT-P41 1.2 and CT-P41 3.1 demonstrated that the ADA status or titre had no impact on PK, PD, efficacy or safety.

3.3. Uncertainties and limitations about biosimilarity

Quality

None.

Non-clinical

No issues were identified.

Clinical PK/PD

Study CT-P41 1.1

PK/PD

No uncertainties or limitations. The study was a small descriptive study with safety as a primary objective.

Study CT-P41 1.2

PK

No uncertainties or limitations.

PD

For secondary PD endpoint (area under the effect curve (AUEC) of serum type 1 C-telopeptide (s-CTX), no uncertainties or limitations were identified.

Regarding the secondary endpoint (percent change from baseline of s-CTX and P1NP at each study visit), the s-CTX concentration returns faster (curves separate at D141) in the US-Prolia group to the baseline after cessation of the drug effect.

Study CT-P41 3.1

PK

No uncertainties or limitations.

PD

For the co-primary PD endpoint s-CTX AUEC over the initial 6 months in FAS population the 95% CI excludes unity for the ratio. Although statistically significant, the Geometric LS Mean Ratio of 94.94% with the corresponding 95% CI was entirely within the predefined equivalence margin of 80%−125% (94.94 [95% CI: 90.75, 99.32]). Therefore, even if there is a difference, it would not be clinically relevant.

Regarding the secondary endpoint, AUEC for P1NP over the initial 6 months, the geometric LS means in PD set were 7663.9 and 9119.8 in CT-P41 and US-Prolia group, respectively. The geometric LS mean ratio was 84.04 with the 95% CI between 73.23 and 96.43. Thus, the conventional range between 80% and 125% was not met, the lower limit of confidence interval being below the lower acceptance boundary. Furthermore, the unity was not reached for the ratio. Contrary to this finding in PMO patients, no difference was observed in the HV study 1.2. The difference may have been driven by 4 patients in the CT-P41 group who exhibited unusually low P1NP AUECs over the initial 6 months. All results indicated that there was no impact from concurrent diseases, baseline characteristics, and PK exposures on the P1NP AUEC of these 4 patients. Therefore, no reason for the difference in outcomes or to exclude these patients was found. The GMR result under discussion could be considered to be largely a result of an artefact created by the data derivation, since the "raw" P1NP values do not raise concern about a difference between the products. Therefore, this issue was not pursued further. At 26-week extension period (Treatment period II), the s-CTX level in the US-Prolia group seems to return to the baseline level faster than in the CT-P41 group. Similar trend, although smaller in size, was seen also closer to Week 52 at the period of waning of the drug effect after the second dose. This is considered a chance finding as the terminal elimination phase is considered less sensitive for biosimilarity as the measurement errors and variability increases.

Efficacy

Study CT-P41 3.1

In FAS, Week 52 LS-BMD change from baseline is available for 222 and 212 patients (CT P41 and US-Prolia, respectively) and 215 and 202 patients in the PPS. This implies that from all participants with observed primary efficacy endpoint a total of 7 and 10 patients, respectively, were excluded from the PPS (8 due to prohibited medication, 2 due inc/exc criteria), while the remaining 7 patients were excluded for not having received study medication at Week 26. Based on the data provided by the applicant, it can be concluded that the frequency of study visits that occurred out of the visit window (OOW) or were missed at certain timepoint and average of their occurrence was similar between groups and no significant difference between groups regarding OOW event was seen. The majority of OOWs occurred after W26 not interfering the co-primary PD endpoint evaluation. The applicant clarifies no specific patterns were shown and trends were similar between the treatment groups. According to the provided data the frequency of the OOW events and missing data in each visit time point at TP I seems to equally distribute between visits. The same is true for TP II.

The rate of discontinuation was higher in US-Prolia with 201 patients (84.1%) completing TPI, while the respective figure in CT-P41 group was 221 patients (92.1%). The applicant was requested to clarify and analyse whether any correlation between withdrawals and efficacy or association with safety/tolerability was present. Based on the applicants response the main reason for the treatment discontinuation, and the difference between treatment groups therein, was patient's decision. However, no data were provided on the objective efficacy measures among those that withdrew prematurely. The applicant states that if treatment discontinuation was decided due to an issue related to efficacy, then disease progression would have been selected as primary reason of treatment discontinuation. This is not necessarily true: Having initiated a treatment with the expectation to gain approximately +5% BMD over a year, the patient and the treating physician might question treatment continuation after 6 months if BMD is not on the expected trajectory (e.g., has not changed from baseline). Such a situation would not necessarily be recorded as "disease progression" that happened on a specific "date of progression". However, the sensitivity analysis data showed no impact of discontinuations on the interpretation of the similarity in efficacy outcome.

Quite large number of visits, 103 in 39 patients, were affected by the war in Ukraine. The primary efficacy and PD analysis was requested to be performed on the PPS excluding patients with treatment discontinuation, rescue medication, study drug administration or study assessments delayed due to COVID-19 infection or the conflict in Ukraine. Based on the "modified PPS analysis" for %cfb in LS-BMD at Week 52, the point estimate was 4.8760 (0.33542) and 5.1676 (0.35919) in the CT-P41 and US-licensed Prolia groups, respectively. The LS mean difference between compared groups with 95% confidence intervals (CIs) was -0.292 [-1.041, 0.458]. These results did not change the initial interpretation of the study outcome and were in line with the primary efficacy analysis in PPS. The same was true for the co-primary PD endpoint with the 95% CI for the geometric being contained within the predefined equivalence margin (95%CI; 89.97, 99.82), in line with the initial analysis outcome for co-primary PD endpoint. The applicant clarifies the proportion of patients being excluded from the analysis set (PPS only) to have been similar between treatment groups.

Safety

In the pilot study CT-P41 1.1 (n=30, 15 in each group), TEAEs were reported for 6 (40.0%) and 12 (80.0%) subjects in the CT-P41 and EU-Prolia groups, respectively. Of these, TEAEs considered related to study drug by the investigator were reported in 3/15 subjects (20.0%) in the CT-P41 treatment group and 6/15 subjects (40.0%) in the EU-approved Prolia treatment group. The more favourable safety profile of CT-P41 vs. EU-Prolia in this small pilot study is likely to be due to chance, taking in

account the similar safety profile of CT-P41 and US-Prolia in healthy male subjects in Study CT-P41 1.2 (N=151, CT-P41 n=74, US-Prolia n=77).

During the Overall period of the Phase 3 study CT-P41 3.1 in women with postmenopausal osteoporosis, an imbalance was observed in the rate of infections. TEAEs of infections were reported for 46.4% of patients in the CT-P41 group, 37.8% of patients in the US-Prolia group, 36.0% of patients in the US-Prolia Maintenance group and 46.5% of patients in the Switched to CT-P41 group. E.g., upper respiratory tract infections and urinary tract infections were more common during treatment with CT-P41. These events are a known risk that is included in Section 4.8 of the Prolia SmPC as common AEs. There were, e.g., also more oral herpes cases in the CT-P41 group. The overall severity of infection related TEAEs was either Grade 1 or 2 and only 6 cases were assessed as related to the study drug out of 338 TEAEs classified as infections.

Upon request, the applicant analysed further the infections and especially opportunistic infections in the study. The difference in the incidence of upper respiratory tract infections and urinary tract infections contributed to the overall difference in the incidence of infections. No clear reason for the differential occurrence of infections in study arms was identified; except that according to post-hoc analyses, there appears to have been more subjects susceptible to infections in the subjects reporting infections CT-P41 group. A total of 13 events (about 3.8% of all infection events) were categorised as opportunistic infections (TP I: 5 and 2 events from CT-P41 and US-licensed Prolia groups, respectively; and TP II: 3, 1, and 2 events from CT-P41 Maintenance, US-licensed Prolia Maintenance, and Switched to CT-P41 groups, respectively). These included herpes zoster, respiratory syncytial virus infection, pneumonia, vulvovaginal mycotic infection, and staphylococcal skin infection. Pneumonia is not generally classified as an opportunistic infection, but it has been conservatively included due to the lack of causative pathogens information. There were no cases of tuberculosis reported in the study. All opportunistic infections were non-serious and either Grade 1 or 2 in severity. No new infection AEs were identified that would warrant update of the Product Information. Taking in account the similar PK, PD and efficacy profile of CT-P41 and US-Prolia, the relatively small imbalance in infections is likely due to chance.

Comparative safety information between CT-P41 and EU-Prolia is scarce, only available from the small pilot study CT-P41 1.1. Studies CT-P41 1.2 and CT-P41 3.1 were conducted with US-Prolia as comparator. No studies were conducted comparing CT-P41 to Xgeva. Obtained data with US-Prolia as comparator can however be extrapolated to similar clinical effects of CT-P41 compared with EU-Prolia and with Xgeva, since analytical similarity of CT-P41 has been demonstrated in a 3-way analytical similarity assessment using EU-authorised as well as US-licensed Prolia and Xgeva.

3.4. Discussion on biosimilarity

Quality

The totality of the presented biological and physiochemical data supports the claim of Biosimilarity for CT-P41 and EU-Prolia/Xgeva. All biological activities relevant to the primary mechanism of action, including osteoclastogenesis inhibition assay, RANKL binding inhibition assay (with OPG / RANK), RANKL binding assay and cell-based RANKL binding assay, are similar. A lower binding activity of CT-P41 to FcγRIIIa (158V and 158F) compared to EU-Prolia/Xgeva was observed and attributed to lower levels for afucosylated glycans and lower level of high mannose glycans in CT-P41. These differences are not considered to be clinically meaningful based on the similar lack of ADCC activity for both CT-P41 and EU-Prolia. Also, differences in PK studies between the proposed biosimilar and the US-reference product were not seen and the mannosylation levels in US- and EU-reference products are

similar. The observed difference in mannosylation is not expected to have an effect on clinical performance.

Differences were also observed in heavy chain deamidation and oxidation, C-terminal lysine and proline amidation and consequently in cIEF peak pattern and IEC-HPLC peak ratios. Furthermore, minor differences were observed in glycation levels and NGHC levels in CT-P41 compared to reference medicinal product. These differences are considered not to be clinically relevant. All observed differences are well discussed and justified, are not considered to be clinically meaningful, and are unlikely to have an impact on PK, efficacy, or safety.

Non-clinical

From the non-clinical point of view, no other concerns or major objections were identified. The *in vivo* study comparing the toxicology and toxicokinetics of CT-P41 60 mg/mL and US-Prolia supported the claim that there are no significant clinically relevant differences between the biosimilar CT-P41 70 mg/mL and the reference medicinal product.

Clinical PK/PD

PK

In the small pilot study CT-P41 1.1 conducted in healthy male subjects with the 60 mg SC dose, the studied PK parameters were comparable. In pivotal PK study CT-P41 1.2 in healthy male subjects with the SC 60 mg dose, PK similarity was demonstrated between CT-P41 and US-Prolia. For the primary PK parameters $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max}, the 90%CI for the ratio of the test and comparator product fell within the pre-specified acceptance range of 0.80-1.25. Thus, all primary PK endpoints were met. This was supported by similar summary statistics of other PK parameters in the study. PK data from study CT-P41 3.1 conducted in female osteoporosis patients with the 60 mg SC dose further supported PK similarity of the test and comparator product. The serum concentrations up to week 78 were very comparable. The summary statistics of studied PK parameters supported the PK similarity between CT-P41 and US-Prolia.

PD

The pivotal Phase 3 study (CT-P41 3.1) **co-primary PD endpoint**, s-CTX AUEC over the initial 6 months in women with postmenopausal osteoporosis (FAS population), met the equivalence criteria with the 95% CI for the ratio of LS geometric mean being entirely within the acceptance range 80 to 125%. However, unity was not included in the 95% CI for the ratio, although being close to value 1. Since a clear margin to the acceptance range boundaries was present for the geometric mean ratio 95% CI, the issue is not pursued further. The time-concentration curves for the arithmetic mean values measured in each visit to clinics were overlapping between the CT-P41 and US-Prolia groups. The Phase 1 CT-P41 1.2 study in healthy male volunteers supported further the PD comparability between the CT-P41 and US-Prolia products, the 95% CI for the ratio of LS geometric mean for the secondary PD endpoints, s-CTX and P1NP AUEC over the study period, being within the conventional acceptance criteria of 80 to 125%. The CI for both biomarkers contained also unity.

Efficacy

The similarity in efficacy was shown in Phase 3 study CT-P41 3.1 in the co-primary efficacy endpoint, %CfB in LS-BMD at Week 52 (FAS population), with the LS mean difference between the groups being

-0.139 (95% CI -0.826, 0.548) and meeting the pre-specified equivalence range of ±1.503% with a clear margin. The clinical justification of the suggested equivalence margin was not presented. However, as the 95% CI for the difference between treatments was very narrow, this issue is not pursued further.

Secondary efficacy results showed that the %CfB in BMD for lumbar spine, total hip, and femoral neck by DXA were similar between the CT-P41 and US-Prolia group. In general, frequency of new vertebral, total hip or femoral neck fractures was low for all treatment groups. Also, for majority of patients, no shift was noted in the semi-quantitative grade for vertebral fractures at Week 78 compared to baseline.

Also, both QoL questionnaires have shown similar outcomes between treatment groups.

Thus, the pivotal Phase 3 study supports the clinical equivalence of CT-P41 against US-Prolia. In a sensitivity study conducted in ITT population provided similar results meeting the pre-specified similarity criterion. Based on the sensitivity analysis, it is very unlikely that the conclusion of equivalence would have been any different had all randomised patients been assessed for Week 52 BMD regardless of treatment discontinuation. Even when considering the possibility that treatment discontinuation would have a different impact depending on whether US-Prolia or CT-P41 was discontinued, a shift as high as +10 (%CfB in BMD) in one group and no shift in the other is required to question the conclusion on equivalence.

Furthermore, the applicant was requested to clarify and analyse whether any correlation between the withdrawals and efficacy or association with safety/tolerability was present. Based on the applicants response the main reason for the treatment discontinuation, and the difference between treatment groups therein, was patient's decision. However, no data were provided on the objective efficacy measures among those that withdrew prematurely. Furthermore, the sensitivity analysis data showed no impact of discontinuations on the interpretation of the similarity in efficacy outcome.

Safety

Comparative safety data between CT-P41 and EU-Prolia are only available from the small pilot study CT-P41 1.1 (n=30), in which the safety profile of CT-P41 appeared more favourable than that of EU-Prolia: TEAEs were reported for 6/15 (40.0%) and 12/15 (80.0%) subjects in the CT-P41 and EU-Prolia groups, respectively. In study CT-P41 1.2, however, the safety profile of CT-P41 and US-Prolia was similar, with 282 TEAEs reported from 114/151 (75.5%) subjects, of which 55/74 (74.3%) and 59/77 (76.6%) of subjects in the CT-P41 and US-Prolia treatment groups, respectively. Therefore, the noted difference in study CT-P41 1.1 could be due to chance.

An overall comparable safety profile was observed in female patients with postmenopausal osteoporosis in Study CT-P41 3.1. The total number (%) of patients with ≥1 TEAE was during TP1 193/239 (80.8%) in the CT-P41 group and 183/238 (76.9%) in the US-Prolia group; and during TP2, 177/220 (80.5%) in the CT-P41 Maintenance group, 75/100 (75.0%) in the US-Prolia Maintenance group, and 82/101 (81.2%) in the Switched to CT-P41 group. The frequencies of reported TEAEs in different SOCs and PTs were overall mostly similar in the Overall period results; but an imbalance was noted in the rate of infections in favour of US-Prolia: 111/239 (46.4%), 102/220 (46.4%), 90 (37.8%), 36 (36.0%), and 47 (46.5%) in the CT-P41, CT-P41 Maintenance, US-Prolia, US-Prolia Maintenance and Switched to CT-P41 groups, respectively. This difference was partly driven by upper respiratory tract and urinary tract infections, both included in Section 4.8 of the Prolia SmPC as common adverse reactions. The applicant investigated the issue further, and no clear reason for the differential occurrence of infections in study arms was identified; except that according to post-hoc analyses, there appears to have been more subjects susceptible to infections among the subjects reporting infections

in the CT-P41 group. Opportunistic infections accounted for 3.8% of all infections, and their distribution was comparable across study groups. Overall, a diverse range of infections was captured during the study, but most infection events were mild and non-serious. No new infection events were identified that would warrant update of Product Information.

The immunological profile of CT-P41 was similar with EU-Prolia in Study CT-P41 1.1 and with US-Prolia in studies CT-P41 1.2 and CT-P41 3.1. Close to all subjects turned ADA positive during clinical trials, mostly with low titres. Few healthy subjects and no PMO patients had NAb. No impact by ADA or NAb was seen in PK,PD, efficacy or safety.

In summary, the clinical data available from the appropriate study setting supports currently the biosimilarity between CT-P41 and US-Prolia.

3.5. Extrapolation of safety and efficacy

CT-P41 was developed as a biosimilar product to Prolia and Xgeva. The mechanism of action of denosumab is identical across the different indications, both for primary and secondary osteoporosis as well as local bone affection around metastases. Denosumab targets and binds with high specificity to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. This prevents the activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone (Prolia USPI; Xgeva USPI; Hanley et al., 2012; Dougall, 2012). Similarly, giant cell tumours of bone consist of stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK receptor, and signalling through the RANK receptor contributes to osteolysis and tumour growth. The mechanism of action is discussed in many reports and scientific publications (Prolia EPAR, Xgeva EPAR; FDA Prolia Medical Review, 2010; FDA Xgeva Medical Review, 2013; Ono et al., 2020; Noji et al., 2023; Casimiro et al., 2021; Lu et al., 2023; Sekigahara et al., 2022). As a summary, the same mechanism underlies in all indications for both products, EU- Prolia and EU-XGEVA.

The pharmacokinetics are also similar, independent of indication, except for some differences in trough concentrations observed across different tumour types. However, these are not likely to have an impact on efficacy. In published studies in advanced cancers with bone metastases neither tumour type nor type of concomitant therapy markedly affected denosumab pharmacokinetics or pharmacodynamics (Sohn W et al., Br J Clin Pharmacal. 2014 Sep; 78(3): 477–487). The pharmacokinetics were seen to correspond well with the data on dose-relatedness in healthy adult volunteers at doses 60 mg and higher (Sohn W et al., 2014). Thus, independent of indication, the PK/PD data obtained from healthy volunteers can be extrapolated to different indications approved for denosumab.

The safety profile of denosumab is in general consistent across all licensed indications and low immunogenicity potential of less than 1% has been described, without meaningful potential to develop neutralising antibodies. The positivity to drug-binding antibodies (<1 %) did not have consequences for the PK, PD, safety profile or clinical response (Prolia SPC). Regarding safety, low levels of calcium in the blood (hypocalcaemia) have been observed during the treatment and are related to the mode of action; high levels (rebound effect) have been observed after stopping the treatment, particularly at high 120 mg doses in patients with giant cell tumour of bone. Multiple vertebral fractures (MVF) have been observed after discontinuation of a high denosumab dose. Except for the aforementioned, in general, there are no notable differences between osteoporosis-related and malignancy indications for

the majority of product-related AEs and the overall safety profile appears similar, independent of indications.

The selected population for the Phase 3 trial (Study CT-P41 3.1), postmenopausal women with osteoporosis, is a sensitive and homogeneous target population to allow the detection of differences between treatment arms. The demonstration of clinical similarity in this population will allow extrapolation to all indications approved for the innovator products together with comparable PK/PD profile in healthy adult volunteers (Study CT-P41 1.2).

3.6. Additional considerations

Not applicable

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Osenvelt is considered biosimilar to XGEVA. Therefore, a benefit/risk balance comparable to the reference product is 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 Osenvelt 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 restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

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.