BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	BLA 351(k)
Application Number	BLA 761404
Received Date	11/30/2023
BsUFA Goal Date	2/28/2025
Division/Office	Division of General Endocrinology/Office of Cardiology, Hematology, Endocrinology and Nephrology Division of Oncology 1/Office of Oncologic Diseases
Review Completion Date	See DARRTS stamped date
Product Code Name	CT-P41
Proposed Nonproprietary Name[1]	denosumab-bmwo
Proposed Proprietary Name[1]	Stoboclo (proposed [redacted] biosimilar to US-Prolia); Osenvelt (proposed [redacted] biosimilar to US-Xgeva)
Pharmacologic Class	RANK Ligand (RANKL) Inhibitor
Applicant	Celltrion Pharmaceuticals
Applicant Proposed Indication(s)	Stoboclo (proposed [redacted] biosimilar to US-Prolia): • Treatment of postmenopausal women with osteoporosis at high risk for fracture. • Treatment to increase bone mass in men with osteoporosis at high risk for fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. • Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. • Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. • Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. Osenvelt (proposed [redacted] biosimilar to US-Xgeva): • Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. • Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or

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

	where surgical resection is likely to result in severe morbidity. • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.
Recommendation on Regulatory Action	Approval of CT-P41 as a biosimilar to US-Prolia and US-Xgeva. (b) (4)

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OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OPQA = Office of Pharmaceutical Quality Assessment
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRM = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health
DPV = Division of Pharmacovigilance
DMPP = Division of Medical Policy Programs
OTBB – Office of Therapeutic Biologics and Biosimilars

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
ANCOVA	Analysis of covariance
AUEC	Area Under the Effect Curve
BLA	Biologics License Application
BMD	Bone Mineral Density
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CA	Comparative analysis
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CfB	Change from Baseline
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CUHF	Comparative Use Human Factors
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DFA	Difference from Theoretical
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
ECLIA	Electrochemiluminescence Immunoassay
FAS	Full analysis set
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
HF	Human Factors
ICH	International Conference on Harmonization

IND	Investigational New Drug
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
MAR	Missing at random
mITT	Modified Intention to Treat
MOA	Mechanism of Action
MSD-ECL	Meso Scale Discovery-Electrochemiluminescent
MSD-SA	Meso Scale Discovery-Streptavidin
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
P1NP	N-terminal propeptide of type I procollagen
PeRC	Pediatric Review Committee
PFS	Pre-filled syringe
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMO	Post-menopausal osteoporosis
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
RLU	Relative Light Units
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
s-CTX	C-terminal telopeptide of type I collagen
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
TK	Toxicokinetics
TP1	Treatment period 1
TP2	Treatment period 2

ULOQ	Upper Limit of Quantitation
URRA	Use-related risk analysis
U.S.-Prolia	U.S.-licensed Prolia
U.S.- Xgeva	U.S. licensed Xgeva

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1 Executive Summary

1.1 Product Introduction

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

The Applicant proposes CT-P41 as an (b) (4) biosimilar product to US-Prolia and US-Xgeva, and the proposed proprietary names are Stoboclo and Osenvelt, respectively.

The Applicant seeks the same indications for CT-P41 as those which are approved for US-Prolia and US-Xgeva. The strengths, dosage form, route of administration, indications, and dosing regimens for CT-P41 will be the same as those of US-Prolia and US-Xgeva, which are listed below:

Stoboclo:

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

- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

Osenvelt

- Strength: 120 mg/1.7 mL
- Dosage form: Injection
- Route of administration: subcutaneous
- Indications and associated dosing regimen:
  - Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors (120 mg injected subcutaneously [SC] every 4 weeks)
  - Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (120 mg injected SC every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy)
  - Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy (120 mg injected SC every 4 weeks with addition 120 mg doses on Days 8 and 15 of the first month of therapy).

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

Not applicable

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

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

This BLA contains sufficient data and information to demonstrate that CT-P41 has the same mechanism(s) of action as those of U.S.-Prolia and US-Xgeva. The Applicant performed a comparative analytical assessment of CT-P41 and US-Prolia and US-Xgeva. The data provided support the conclusion that CT-P41 is highly similar to US-Prolia and US-Xgeva.

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

CT-P41 is proposed as below:

For subcutaneous injection:

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

CT-P41 also has the same dosage form, strengths, and route of administration as those of US-Prolia and US-Xgeva.

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

1.4 Inspection of Manufacturing Facilities

The Office of Product Quality (OPQ) has conducted the manufacture facility assessment and recommended inspection waiver at Celltrion Inc (FEI: 3005241015), listed in this application as the CT-P41 drug substance (DS) manufacture facility, at (b) (4) listed as the CT-P41 PFS drug product (DP) manufacture facility, as well as at (b) (4), listed as CT-P41 vial drug product (DP) manufacture facility. The recommendation is based on that there has been FDA and/or MRA inspection within the last two years, and all proposed manufacturing facilities are acceptable based on their current cGMP compliant status and relevant inspectional coverage.

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

Not Applicable.

1.6 Biosimilarity (b) (4) Assessment

Table 1. Summary and Assessment of Biosimilarity (b) (4)

Comparative Analytical Studies[2]	
Summary of Evidence	• The comparative analytical assessment included comparisons between CT-P41, US-Prolia and US-Xgeva. • CT-P41 is highly similar to US-Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components • CT-P41 has the same strengths, dosage form, and route of administration as US-Prolia and US-Xgeva.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies	
Summary of Evidence	• The information in the pharmacology/toxicology assessment supports the demonstration of biosimilarity
Assessment of Residual Uncertainties	• There are no residual uncertainties from the pharmacology/toxicology assessment
Clinical Studies	
Clinical Pharmacology Studies	
Summary of Evidence	• Pharmacokinetic (PK) similarity between CT-P41 and US-Prolia was demonstrated in healthy male subjects in Study CT-P41 1.2 (hereinafter referred to as Study 1.2) and supports a demonstration of no clinically meaningful differences between CT-P41 and US-Prolia. • Because of demonstrated analytic similarity between CT-P41 and US-Xgeva and US-Prolia, PK data from Study 1.2 also support the conclusion that CT-P41 would be expected to have similar PK as US-Xgeva. • The presence of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were compared between CT-P41 and US-Prolia in healthy male

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

	subjects in Study 1.2 and in female subjects with postmenopausal osteoporosis in Study CT-P41 3.1 (hereinafter referred to as Study 3.1). There was similar incidence of immunogenicity between study arms for each study and no clinically relevant impact of immunogenicity was observed. Therefore, the data support that CT-P41 has no clinically meaningful differences from US-Prolia. • Immunogenicity data from studies 1.2 and 3.1 support the conclusion that CT-P41 would be expected to have similar immunogenicity as US-Xgeva.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical pharmacology perspective.
Comparative Clinical Studies	
Summary of Evidence	• The Applicant conducted a randomized, double-blind comparative clinical study (Study 3.1) in 477 post-menopausal women with osteoporosis to compare the PK, pharmacodynamics (PD), efficacy, safety and immunogenicity of CT-P41 and US-Prolia. Four-hundred and seventy-nine female subjects were randomized to receive CT-P41 or US-Prolia 60 mg injected subcutaneously (SC) every six months for one year (Treatment period 1). After one year, subjects initially assigned to US-Prolia in Treatment period 1 were re-randomized to either continue US-Prolia or transition to CT-P41. Subjects who received CT-P41 in Treatment period 1 continued their treatment with CT-P41. Subjects were followed for six months after the third dose of study drug. • This study demonstrated that CT-P41 and U.S.-Prolia have similar efficacy with respect to the percent change from baseline in bone mineral density (BMD) for lumbar spine at Week 52. The 90% confidence interval (CI) for the difference in mean change were within the pre-specified equivalence margin of ±1.45%. The study support the demonstration there is no clinically meaningful differences between CT-P41 and US-Prolia. • The safety profiles of CT-P41 and U.S.-Prolia were comparable. The adverse events observed

	were consistent with the known safety profile of denosumab (as labeled in the U.S.-Prolia USPI). There were no meaningful differences in the incidence of specific adverse events between CT-P41 and U.S.-Prolia, and the small differences in incidences of some of the treatment emergent adverse events (TEAE) that were observed in the CT-P41 and U.S.-Prolia arms was likely due to chance. Subjects transitioning from U.S.-Prolia to CT-P41 experienced a greater incidence of upper respiratory infections (11%) compared to subjects continued on U.S.-Prolia (4%) or CT-P41 (6%). These differences were also likely due to chance, and likely do not represent a clinically meaningful safety difference. • The study also demonstrated similarity of CT-P41 and U.S.-Prolia with respect to the pharmacokinetics of denosumab, pharmacodynamic effect on biomarkers of bone turnover, and immunogenicity.
Assessment of Residual Uncertainties	• There are no residual uncertainties.
[redacted] (b) (4)	
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.

Any Given Patient Evaluation	
Summary of Evidence	• The Applicant has provided adequate data and information, including the analytical and clinical data, to support a demonstration that CT-P41 can be expected to produce the same clinical result as that of US-Prolia and US-Xgeva in any given patient.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Extrapolation	
Summary of Evidence	• Division of General Endocrinology (DGE) and the Office of Oncology Drugs (OOD) have determined that the Applicant has provided adequate scientific justification and agrees with the applicant's justification for extrapolation to the other indications listed in the US-Prolia and US-Xgeva USPIs being sought for licensure based on: 1) the mechanism of action of denosumab, 2) the analysis of the known safety and immunogenicity profiles of denosumab across each of the indications being sought and 3) the assessment of any differences in expected toxicities for each indication. • The data and information submitted by the Applicant, including the justification for extrapolation, supports licensure of CT-41 as (b) (4) biosimilar to US-Prolia and US-Xgeva for the following indications for which US-Prolia and US-Xgeva have been previously approved: ○ Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures. ○ Treatment to increase bone mass in men with osteoporosis, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

	○ Treatment of glucocorticoid-induced osteoporosis who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. ○ Treatment to increase bone mass in men at high for fracture receiving androgen deprivation therapy for prostate cancer ○ Treatment to increase bone mass in women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer ○ Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors ○ Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity ○ Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of CT-P41 as (b) (4) biosimilar to US-Prolia and US-Xgeva for the above indications.

1.7 Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that CT-P41 is highly similar to U.S.-Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between CT-P41 and U.S.-Prolia, or between CT-P41 and US-Xgeva in terms of the safety, purity, and potency of the product. The data and information provided by the Applicant are sufficient to demonstrate that CT-P41 can be expected to produce the same clinical result as U.S.- Prolia and U.S.-Xgeva in any given patient, (b) (4)

(b) (4)

The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that CT-P41 is biosimilar to US-

Prolia and US-Xgeva [redacted] follows:

- CT-P41, 60 mg/mL injection for SC use in a single-dose PFS as [redacted] biosimilar to US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS,
- CT-P41, 120 mg/1.7 mL injection for SC use in a single-dose vial as [redacted] biosimilar to US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial,

for each of the following indications for which US-Prolia and US-Xgeva have been previously approved and for which the Applicant is seeking licensure of CT-P41:

U.S.-Prolia:

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

U.S.-Xgeva:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

[redacted]

(b) (4)

Therefore, BLA 761404 will be administratively split to facilitate an approval action for CT-P41 as biosimilar to US-Prolia and US-Xgeva ("Original 1") (b) (4)

The review team recommends approval of CT-P41 as a biosimilar product as follows:

- CT-P41, 60 mg/mL injection for SC use in a single-dose PFS is biosimilar to US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS,
- CT-P41, 120 mg/1.7 mL injection for SC use in a single-dose vial is biosimilar to US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial.

(b) (4)

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

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2 Introduction and Regulatory Background

2.1 Summary of Presubmission Regulatory History Related to Submission

Pre-IND 147751 for this product was opened in March 2020, with submission of a Biosimilar Biological Product Development (BPD) Type 2 meeting request. The initial BPD Type 2 meeting occurred on May 27, 2020, to discuss the proposed quality, non-

clinical and clinical program for development of CT-P41 as a biosimilar product to US-licensed Prolia and US-licensed Xgeva.

The Applicant opened IND 147751 on October 14, 2020, with submission of Protocol CP-P41 3.1 for a comparative clinical study. The submission included a request for special protocol assessment. FDA considered the study to be safe to proceed but denied the SPA request because of disagreement with the proposed imputation method in the primary efficacy analysis plan. These and subsequent interactions with FDA are summarized in **Table 2**.

Table 2. Regulatory Milestones

Date	Event	Comments
May 27, 2020	BPD Type 2 meeting	FDA advised that if comparative clinical data obtained using an EU-approved comparator, relevance of these data should be justified and scientific bridge to the US-licensed reference product established
October 14, 2020	IND 147751 opened: • Protocol CP-P41 3.1 for comparative clinical study; submitted along with request for special protocol assessment (SPA)	FDA issued a Study safe to proceed letter but denied SPA
November 24, 2020	SPA denial letter	FDA disagreed with plan to manage missing data for primary efficacy analysis
October 22, 2021	BPD Type 2 meeting	FDA continued disagreement with proposal for managing missing data for primary efficacy analysis
May 4, 2022	Submission of revised statistical analysis plan (SAP) for comparative clinical study protocol CT-P41 3.1	Discussed the revised plan to manage missing data
December 21, 2022	Initial pediatric study plan (iPSP)	Agreed upon iPSP sent to Applicant
November 09, 2022	Advice letter from FDA	(b) (4)

Date	Event	Comments
June 01, 2023	Advice letter from FDA	(b) (4) [redacted]
June 27, 2023	BPD Type 4 meeting	Discussed planned 351(k) BLA submission

2.2 Studies Submitted by the Applicant

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

Non-clinical and clinical studies submitted in support of biosimilarity (b) (4) [redacted] of CT-P41 are summarized in **Table 3** and **Table 4**, respectively.

Table 3: Animal Study Submitted †

Study Title	Study Number	Species	Number Per Treatment Arm	Study Duration	Route of administration/Dose
Animal Studies					
CT-P41 and US-Prolia: 4-Week Subcutaneous Injection Toxicity and Toxicokinetic Study in Cynomolgus Monkeys	1878-035	Cynomolgus Monkey	3/sex	4 weeks	SC, 0 or 10mg/kg CT-P41 or US-Prolia once weekly

Table 4. Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study					
CT-P41 1.2	N/A	A PK similarity study to compare pharmacokinetics and safety of CT-P41 and US-Prolia	Double-blind, randomized, two-arm, parallel-group, single dose	Healthy Subjects	CT-P41 (N=76) US-Prolia (N=78)

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
Comparative Clinical Study(ies)					
CT-P41 1.1	N/A	A Pilot study to compare safety and pharmacokinetics of CT-P41 and EU-Prolia	Randomized, double-blind, two-arm, parallel group, single-dose	Healthy adult males	CT-P41 (N=16) EU-Prolia (N=16)
CT-P41 3.1	N/A	A comparative clinical study to compare efficacy, pharmacokinetics, pharmacodynamics, immunogenicity and safety of CT-P41 and US-Prolia	Double-blind, randomized, active-controlled, two-part study	Post-menopausal women with osteoporosis	Part I: CT-P41 (N=240) US-Prolia (N=239) Part II: CT-P41 maintenance (N=221) US-Prolia maintenance (N=100) Switch from US-Prolia to CT-P41 (N=101)

The 4-week monkey study (Study 1878-035) was considered supportive of a biosimilarity determination but the animal study was not necessary because in vitro structural comparison and binding analysis plus functional characterization are considered sufficient and more sensitive than animal study to demonstrate biosimilarity of CT-P41 to U.S.-Prolia and U.S.-Xgeva. However, because the animal study was conducted and submitted in the BLA, the study was reviewed and is summarized in Section 4 of this BMER.

Data generated from study CT-P41 1.1, which is a pilot study compared safety of CT-P41 to EU-approved Prolia only, were not used to support a demonstration of biosimilarity. Therefore, the results from data generated with EU-approved Prolia in study CT-P41 1.1 were not assessed.

Authors:

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Primary Nonclinical Reviewer

David Carlson
Nonclinical Reviewer and Supervisor

Olivia Easley
Clinical Reviewer

3 Summary of Conclusions of Other Review Disciplines

3.1 Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Quality (OPQ) is recommending approval of BLA 761404 for CT-P41 manufactured by Celltrion. The data submitted in this application are adequate to support a conclusion that the manufacture of CT-P41 is well-controlled and will lead to a product that is pure and potent.

The Applicant used a comprehensive set of analytical methods that were suitable to evaluate the critical quality attributes of CT-P41 and U.S.-Prolia/ U.S.-Xgeva to support the demonstration that CT-P41 is highly similar to U.S.-Prolia and U.S.-Xgeva notwithstanding minor differences in clinically inactive components. The number of lots tested and data analysis approaches used were appropriate or justified as needed to allow for a meaningful evaluation of the results of the analytical studies. The totality of the evidence from the comparative analytical assessment supports that CT-P41 is highly similar to U.S.-licensed Prolia and U.S.-licensed Xgeva, notwithstanding minor differences in clinically inactive components. The strengths of CT-P41 60 mg/mL in the single-dose PFS for subcutaneous injection and 120mg/1.7mL (70mg/mL) in a single-dose vial for subcutaneous injection are the same as those of US-licensed Prolia and US-licensed Xgeva in the same dosage form and routes of administration, respectively. Refer to the OPQ Executive Summary dated August 14, 2024, and addendum dated February 18, 2025.

3.2 Devices

Stoboclo is supplied as a drug-device combination product, and each prefilled syringe contains 60 mg of CT-P41. Osenvelt is supplied as a single-dose vial, and hence, is not considered a drug-device combination product.

3.2.1 Center for Devices and Radiological Health (CDRH)

The Center for Devices and Radiological Health was consulted for review of the device constituent part of the Stoboclo drug-device combination product.

The device constituent parts of Stoboclo consist of a fixed-dose and single use pre-filled syringe (PFS) with a needle safety guard. The needle safety guard uses the (b) (4) (b) (4), which has 510(K) clearance from CDRH. The device safety guard activation force is (b) (4) N and the lock-out force is (b) (4) N, which were considered acceptable by the CDRH review team. Testing of the relevant force attributes are performed before release. The Applicant has applied the relevant standards (testing and biocompatibility) for the needle safety guard.

The CDRH review team has concluded that the device constituent parts of the combination product are acceptable. Refer to the CDRH consult review dated October 9, 2024, in DARRTS for additional details.

3.2.2 Division of Medication Error Prevention and Analysis (DMEPA)

The Division of Medication Error Prevention and Analysis 1 (DMEPA-1) evaluated the comparative analysis (CA), to determine if Human Factors (HF) Validation study and Comparative Use Human Factors (CUHF) study are required to support the marketing application for CT-P41 as (b) (4) biosimilar to U.S.-Prolia.

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

Refer to the DMEPA-1 review dated September 26, 2024 in DARRTS for additional details.

3.3 Office of Study Integrity and Surveillance (OSIS)

A Biopharmaceutical Inspections Request was sent to OSIS on 1/19/24 (DARRTS Reference ID: 5313537) requesting routine inspections for Study CT-P41 1.2 (Bioequivalence study). The request covered inspections for the Chungnam National University Hospital (clinical site), CHA Bundang Medical Center (clinical site), and (b) (4) (b) (4) (analytical site). The summary of OSIS inspections/ findings include:

- OSIS declined to conduct inspection for the Chungnam National University Hospital as the Office of Regulatory Affairs (ORA) conducted an inspection for the site in June 2023 for BLA 761358. OSIS concluded that the data from the reviewed studies was reliable. (DARRTS Reference ID: 5313537)
- OSIS declined to conduct inspection for the (b) (4) as it had conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4) for NDA (b) (4). OSIS concluded that the data from the reviewed studies was reliable. (DARRTS Reference ID: 5313537)
- The inspection for the clinical site CHA Bundang Medical Center was finalized on November 3rd 2024, and no major deficiency was identified (DARRTS Reference ID: 5474414). OSIS deferred to the Division on the impact of 10 days gap instead of protocol required 2 weeks gap between COVID-19 vaccination and investigational product administration for subject (b) (6) on the data for the audit study CT-P41 1.2. The review team concluded that the deviation is unlikely to impact the reliability of the data from the CHA Bundang Medical Center. Overall, the data from this clinical site is considered reliable.

3.4 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted an inspection of two sites in Poland (Site #2509 [Dr. Edward Czerwinski] and Site #2510 [Krzysztof Szymanowski]), the Sponsor Celltrion, Inc. (Celltrion) and the Contract Research Organization (CRO) (b) (4) for Study CT-P41 3.1. OSI concluded that the data generated by these sites and the primary efficacy endpoint data that were centrally read by the CRO and submitted by the Sponsor appear acceptable in support of the respective indication. Refer to OSI review dated September 6, 2024 in DARRTS for additional details.

Author:
Shivangi Vachhani, MD
Cross Disciplinary Team Leader, DGE

4 Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

Author: Mekonnen Lemma Dechassa, Nonclinical reviewer
Signature: David Carlson, Nonclinical reviewer and Supervisor

4.1 Nonclinical Executive Summary and Recommendation

The Applicant used physiochemical testing and in vitro biological assays to demonstrate that CT-P41 is highly similar to US-Prolia and US-Xgeva (see Section 3.1). The in vitro structural characterization and functional analyses are considered sufficient and more sensitive than animal studies to demonstrate biosimilarity and to detect any functional differences (e.g., in affinity to RANKL and related receptor activity) and toxicities, should they exist, between CT-P41 and US-Prolia or between CT-P41 and US-Xgeva. The biochemical structure and mechanism of action of the denosumab products are the same. Comparative analytical studies and in vitro functional analyses comparing CT-P41 and US- Prolia and US-Xgeva were assessed by the Product Quality discipline.

As part of the Applicant's global development strategy for CT-P41, the Applicant conducted a 4-week repeated dose monkey study. The animal study was intended to demonstrate similarity in toxicity and toxicokinetics (TK) in a pharmacologically relevant species between CT-P41 and US-Prolia when administered 10 mg/kg SC for 4-weeks. The cynomolgus monkey was chosen for the comparative animal study because denosumab is pharmacologically active in monkeys and has been previously used in toxicological studies of US-Prolia. The dose and route of administration were consistent with the currently approved labeling of US-Prolia.

In the absence of physicochemical or bioanalytical differences from the reference product, the Agency did not consider an in vivo comparison necessary to show CT-P41

is highly similar to US-Prolia. However, because the in vivo animal study was conducted and submitted under the IND and with the BLA, the 4-week monkey study was reviewed and is summarized here. In the 4-week monkey study in which CT-P41or US-Prolia was administered at10 mg/kg SC for 4-weeks, there were no differences in toxicokinetic or toxicological profiles. There were no adverse effects on electrocardiography endpoints. The systemic exposures to CT-P41 and US-Prolia were comparable and exposure to both compounds increased after repeated administration. No anti-drug antibodies were detected in animals in either CT-P41 or US-Prolia treated groups. Consistent with the expected pharmacologic activity of denosumab products, comparable mild to moderate decreases in calcium, phosphorus and alkaline phosphatase levels and increases in femur trabecular bone growth were observed in both sexes in both CT-P41 and US-Prolia treated groups. Overall, the 4-week monkey study showed that CT-P41 has similar pharmacodynamic, toxicokinetic, and toxicity profiles to US-Prolia.

While the comparative analytical assessment has established that CT-P41 is highly similar to US-Prolia and US-Xgeva, the nonclinical animal data showed comparable toxicity and systemic exposure profiles for CT-P41 and US-Prolia in support of biosimilarity between CT-P41 and US-Prolia and US-Xgeva.

4.1.1 Nonclinical Residual Uncertainties Assessment

There are no nonclinical residual uncertainties.

4.2 Product Information

CT-P41 60 mg/1 mL drug product in pre-filled syringe and CT-P41 120 mg/1.7 mL drug product in vial are formulated as sterile, preservative free liquid solutions for subcutaneous administration.

Each CT-P41 60 mg drug product is composed of 60 mg CT-P41 (denosumab) drug substance in 1 mL solution with 4.7% sorbitol, (b) (4) acetate, 0.01% polysorbate 20 and water for injection (Table 5). Similarly, each vial of CT-P41 120 mg drug product is composed of 120 mg denosumab drug substance and 4.6% sorbitol, (b) (4) acetate, 0.01% polysorbate 20 and water for injection (Table 6).

The compositions of the CT-P41 drug products are qualitatively and quantitatively comparable to the respective US-reference products. The CT-P41 60 mg PFS drug product has the same qualitative and quantitative formulation as U.S.-Prolia. The formulation of the CT-P41 120mg vial drug product is qualitatively the same as U.S.-Xgeva but differs slightly quantitatively, however, these minor differences do not impact the product quality, safety or potency and prelude a determination that CT-P41 is highly similar to US-Prolia and US-Xgeva. Refer to the OPQ Executive Summary dated August 14, 2024, and addendum dated on February 18, 2025.

Table 5: Composition of the CT-P41 60 mg Drug Product

Ingredient	Quantity/Syringe [1] 60 mg	Function	Grade
CT-P41 (denosumab)	60 mg	Active ingredient	In-house
Acetic Acid	0.26 mg	(b) (4)	Ph. Eur., USP/NF
Sodium Acetate (b) (4)	(b) (4)		Ph. Eur., USP/NF
Sorbitol	47.00 mg		Ph. Eur., USP/NF
Polysorbate 20	0.10 mg		Ph. Eur., USP/NF
Water for Injection	Q.S. to 1.0 mL		Ph. Eur., USP/NF

NF: National Formulary, Ph. Eur.: European Pharmacopeia, Q.S: Quantum Satis, USP: United States Pharmacopeia,
[1] The amount of each component per syringe is the nominal value.
[2] (b) (4) 1.05 mg of sodium acetate per USP monograph definition (anhydrous calculation) for CT-P41 60mg drug product.

Source: SDN #1, Module 3.2.P.1, Applicant Submission

Table 6: Composition of 120 mg CT-P41 Drug Product

Ingredient	Quantity/Vial[1] CT-P41 120 mg	Function	Grade
CT-P41 (denosumab)	120 mg	Active ingredient	In-house
Acetic Acid	0.44 mg	(b) (4)	Ph. Eur., USP/NF
Sodium Acetate (b) (4)	(b) (4)		Ph. Eur., USP/NF
Sorbitol	79.90 mg		Ph. Eur., USP/NF
Polysorbate 20	0.17 mg		Ph. Eur., USP/NF
Water for Injection	QS to 1.7 mL		Ph. Eur., USP/NF

Ph. Eur.: European Pharmacopeia, USP: United States Pharmacopeia, NF: National Formulary, Q.S: Quantum Satis
[1] The amount of each component per vial is nominal value.
[2] (b) (4) 1.78 mg of sodium acetate per USP monograph definition (anhydrous calculation) for CT-P41 120 mg drug product.

Source: SDN #1, Module 3.2.P.2, Applicant Submission

4.3 Comments on Excipients

The excipients in CT-P41 60 mg drug product (PFS) and CT-P41 120 mg drug product (vial) shown in Table 5 and Table 6 are the same and present in similar amounts as the excipients in U.S.-Prolia and US-Xgeva, respectively. All excipients in CT-P41 60 mg PFS and CT-41 120 mg vial are compendial grade. No novel excipients are used in the manufacturing of CT-P41 60 mg DP PFS or CT-41 120 mg DP vial. No toxicological concerns of the excipients were identified.

4.4 Comments on Impurities of Concern

No impurities or degradants of toxicological concern were identified.

Authors:

Mekonnen Lemma Dechassa
Nonclinical Primary Reviewer

David Carlson
Nonclinical Reviewer and Supervisor

5 Clinical Pharmacology Evaluation and Recommendations

Author: Deepa A. Rao, Ph.D., and Li Li, Ph.D.
Signature: Clinical Pharmacology reviewer and Team Leader

5.1 Clinical Pharmacology Executive Summary and Recommendation

Table 7: Clinical Pharmacology Major Review Issues and Recommendations.

Review Issue	Recommendations and Comments
Pharmacokinetics	• PK similarity between CT-P41 and US-Prolia was demonstrated in healthy male subjects (Study 1.2). • PK data from Study 1.2 also support the conclusion that CT-P41 would be expected to have similar PK as US-Xgeva, because comparative PK data generated with the 60 mg/1 mL (US-Prolia) strength are relevant for conclusions about PK similarity for the 120 mg/1.7 mL (US-Xgeva) strength. • Comparable denosumab exposure between CT-P41 and US-Prolia was demonstrated in postmenopausal women with osteoporosis (Study 3.1). • These results support that CT-P41 has no clinically meaningful differences from US-Prolia and US-Xgeva.
Immunogenicity	• The incidence of ADAs and NAbs was similar between CT-P41 and US-Prolia treatment arms in Studies1.2 and 3.1. There was no apparent impact of ADA and NAb on denosumab PK, PD, safety and efficacy. Therefore, the immunogenicity data also support that CT-P41 has no clinically meaningful differences from US-Prolia and US-Xgeva.

The clinical development program of CT-P41 included two clinical studies:

1. Study CT-P41 1.2 (Study 1.2): a randomized, double-blind, two-arm, parallel group, single-dose, "phase I" study to compare the pharmacokinetics, pharmacodynamics, and safety between CT-P41 and US- Prolia in healthy male subjects.

2. Study CT-P41 3.1 (Study 3.1): a double-blind, randomized, active-controlled, "phase 3" study to compare efficacy, pharmacokinetics, pharmacodynamics, and safety of CT-P41 and US- Prolia in postmenopausal women with osteoporosis.

The Clinical Pharmacology review for this BLA primarily focused on the PK similarity study (Study 1.2) and additional PK and immunogenicity data from the comparative clinical study (Study 3.1).

PK similarity between CT-P41 and US-Prolia was demonstrated because the 90% confidence intervals (CIs) for the ratio for CT-P41/US-Prolia of geometric means for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max} were all completely contained within the pre-specified equivalence limits [0.80; 1.25] (**Table 8**).

Table 8. Summary of statistical analyses for assessment of PK similarity (Study 1.2)

Parameter	Geometric Mean (% CV)		Geometric Mean Ratio* (90% CI)
	CT-P41	US Prolia	CT-P41 vs US Prolia
Primary			
$AUC_{0\text{-}\infty}$ (day•µg/mL)	319.4 (24.5%) (n = 74)	297.7 (29.3%) (n = 75)	107.28 (100.39, 114.65)
$AUC_{0\text{-last}}$ (day•µg/mL)	313.8 (23.9%) (n = 72)	293.7 (29.5%) (n = 74)	106.86 (99.92, 114.28)
C_{max} (µg/mL)	5.521 (24.3%) (n = 74)	5.461 (26.7%) (n = 77)	101.09 (95.20, 107.34)

*Presented as percent.
Source: Modified from Applicant analysis Table 11.4, page 79; Study 1.2, Link to Study 1.2 CSR

In addition, study drug concentration time-profiles are highly overlapped between CT-P41 and U.S.-Prolia treatment arms during Treatment Period 1 and Treatment Period 2 in the comparative clinical study (Study 3.1; See Section 5.3.2).

Lastly, the incidence of ADAs and NAbs was similar between CT-P41 and US-Prolia in Study 1.2 and Study 3.1 (see Section 5.4) .

Overall, the submitted clinical pharmacology information supports the demonstration that CT-P41 has no clinically meaningful differences from US-Prolia and US-Xgeva, and add

to the totality of the evidence to support demonstration of biosimilarity between CT-P41 and US-Prolia, and between CT-P41 and US-Xgeva.

5.1.1 Clinical Pharmacology Residual Uncertainties Assessment

There are no residual uncertainties from the clinical pharmacology perspective.

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

Not Applicable

5.3 Human Pharmacokinetic and Pharmacodynamic Studies

5.3.1 STUDY 1.2

Denosumab is a human monoclonal antibody (IgG2) that targets and binds receptor activator of nuclear factor kappa-B ligand (RANKL). Binding of RANKL by denosumab prevents receptor activation and inhibits osteoclast formation. Osteoclasts are responsible for bone resorption and loss of bone mass. Inhibition of osteoclasts leads to an increase in bone mass and strength.

The active ingredient in CT-P41 is denosumab and the Applicant is seeking CT-P41 as (b) (4) biosimilar to US-licensed Prolia, and US-licensed Xgeva.

The clinical development program of CT-P41 included two clinical studies, a PK similarity study (Study 1.2) and a comparative clinical study (Study3.1). The clinical pharmacology review primarily focused on the PK similarity study and additional PK and immunogenicity data from the comparative clinical study. The Applicant submitted PD data from the clinical studies, and these have been included for completeness. However, it should be noted, that the data from the PD analyses were only evaluated to ensure that the findings did not conflict with the results from the primary endpoint and other assessments considered as part of the decision-making regarding the assessment of biosimilarity.

5.3.1.1 Clinical Pharmacology Study Design Features

This is a randomized, double-blind, two-arm, parallel group, single-dose, “Phase I” Study to compare the pharmacokinetics, pharmacodynamics, and safety between CT-P41 and US- Prolia in healthy male subjects.

Study Population:
Healthy male subjects between the ages of 28 and 55 years, with a body mass index (BMI) between 18.5 and 29.9 kg/m^2 and a body weight between 50.0 and 99.9 kg were included in this study. Across both cohorts a total of 154 subjects were enrolled in the study, of which 151 completed. Overall, demographics and baseline characteristics were

similar between the 2 treatment groups. Subjects were stratified according to body weight (< 80 kg vs. ≥ 80 kg) and study center to ensure both factors were well balanced between the 2 treatment groups.

Drug Formulation and Administration:

- CT-P41: 60 mg was administered by SC injection to the upper arm via pre-filled syringe (PFS) as a single administration
- US- Prolia: 60 mg by SC injection to the upper arm via PFS as a single administration.

5.3.1.2 Clinical Pharmacology Study Endpoints

Primary PK Endpoints: Multiple PK samples were collected up to 8.5 months after a single dose administration of CT-P41 and US-Prolia with primary PK endpoints of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}. To demonstrate PK similarity, the 90% CI of the geometric Least Squares mean ratios needs to fall within 80-125%.

PD Endpoints: Area Under the Effect Curve (AUEC) of C-terminal telopeptide of type I collagen (s-CTX), AUEC of N-terminal propeptide of type I procollagen (P1NP), Percent change from baseline (CfB) of s-CTX and P1NP.

PK Datasets Analyzed: Of the original 154 subjects enrolled, 3 subjects discontinued the study due to protocol deviation and withdrawal of consent prior to study drug administration. In the US-Prolia groups, an additional 2 subjects withdrew early. Of the remaining 149 subjects, in the CT-P41 group 74 completed the study, and in the US-Prolia group 75 completed the study. In the PK set that was evaluated from a total of 149 subjects and 146 subjects were included in the analysis of $AUC_{0\text{-}inf}$,$AUC_{0\text{-}last}$, and Cmax respectively.

5.3.1.3 Bioanalytical PK Method and Performance

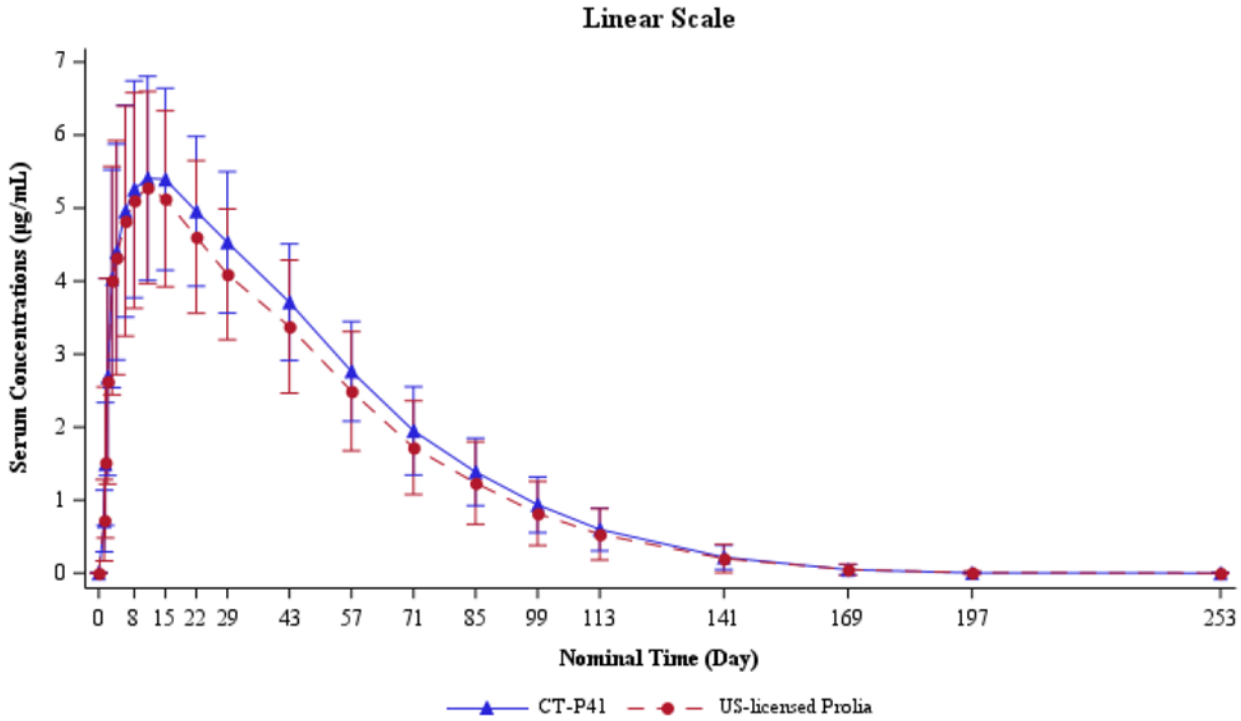
For the PK similarity study (Study 1.2) and comparative clinical study (Study 3.1), serum concentrations of study drugs from CT-P41 and US-Prolia were measured using Meso Scale Discovery-Electrochemiluminescent (MSD-ECL). In this assay, a Meso Scale Discovery -Streptavidin (MSD-SA) coated plate is blocked and then coated with biotinylated-RANKL. CT-P41 or US- Prolia present in samples are captured by biotinylated-RANKL. Sulfo-Tag labeled HCA282 is then used to detect CT-P41 or US-Prolia. In the presence of tripropylamine-containing read buffer, the Sulfo-Tag produces an ECL signal that is triggered when voltage is applied. Only samples that contain antibody bound to both biotinylated-RANKL and Sulfo-Tag labeled HCA282 will generate an ECL signal. The resulting electrochemiluminescence is measured in relative light units (RLU) using the Meso-Scale Discovery (MSD) SECTOR S 600 plate reader.

The method was fully validated for the study drug in accordance with the Bioanalytical Method Validation Guidance from the Agency. Refer to the Appendix 13.2.1 for more detailed information on method validation.

5.3.1.4 PK Similarity Assessment

The mean serum concentration-time profiles are similar between CT-P41 and U.S.-Prolia (Figure 1).

Figure 1: Denosumab serum concentrations vs. time profile (Study CT-P41 1.2)



Source: Figure 11-1, page 80, Study 1.2 , Link to Study 1.2 CSR

The ratios of geometric Least Squares means [90% CI] of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max} were 107.28 [100.39, 114.65], 106.86 [99.92, 114.28], and 101.09 [95.20, 107.34], respectively. The 90% CIs for all primary endpoints were within the equivalence margin of 80% to 125%, indicating the similarity between CT-P41 and US- Prolia in terms of PK (**Table 8**).

5.3.1.5 Bioanalytical PD Method and Performance

Bone turnover markers s-CTX and P1NP in human serum were quantified using the electrochemiluminescence immunoassay (ECLIA) immunoassays from (b) (4) The PD assays are based on commercially available in vitro diagnostic (IVD) kits, that were refined and fully validated with respect to precision, accuracy, parallelism, selectivity, dilution linearity, robustness, carry-over, and tested for stability (short-term, long-term, freeze/thaw cycles). Both the s-CTX and P1NP assays were additionally validated for the use of a 2-point calibration curve. All validation parameters

passed the acceptance criteria, and the assays are considered appropriate for the quantification of s-CTX and P1NP in human serum.

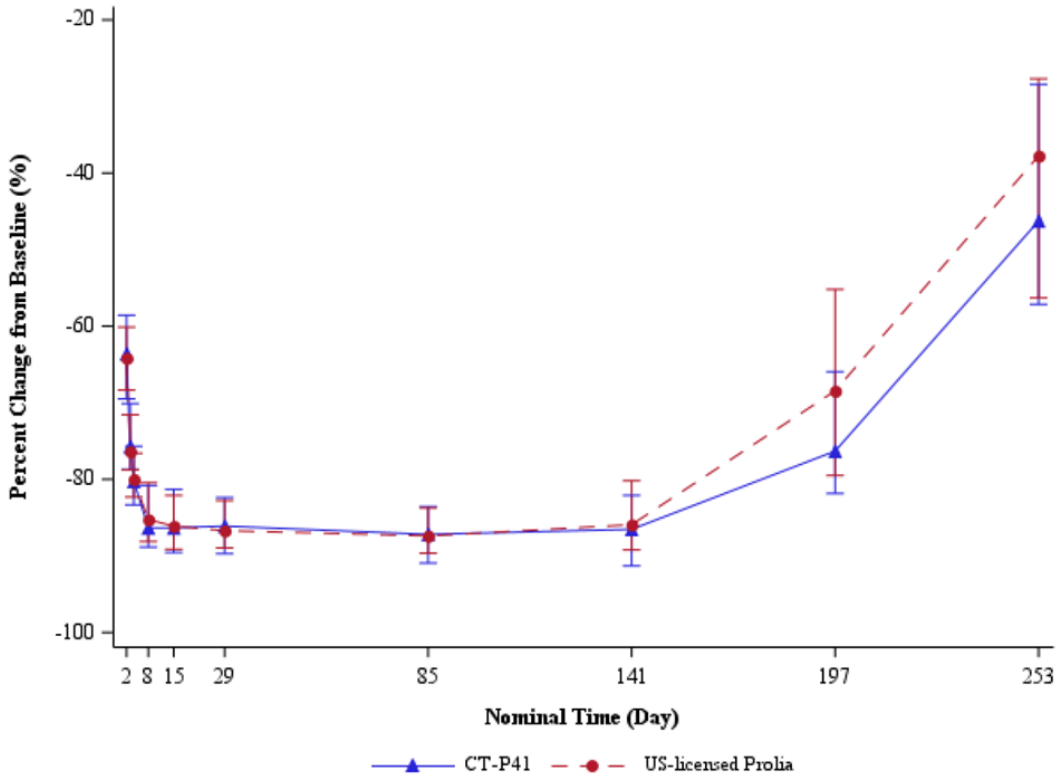
A summary of the bioanalytical validation report to assess the PD markers (s-CTX and P1NP) can be found in the Clinical Pharmacology Appendices (Section13.2.1).

5.3.1.6 PD Similarity Assessment

The Applicant collected and analyzed PD data in the clinical studies, for which the results have been presented for completeness. These data were only evaluated to ensure the findings did not conflict with any of the results from the primary endpoint results and other assessments considered as part of decision-making as it pertains to the assessment of biosimilarity.

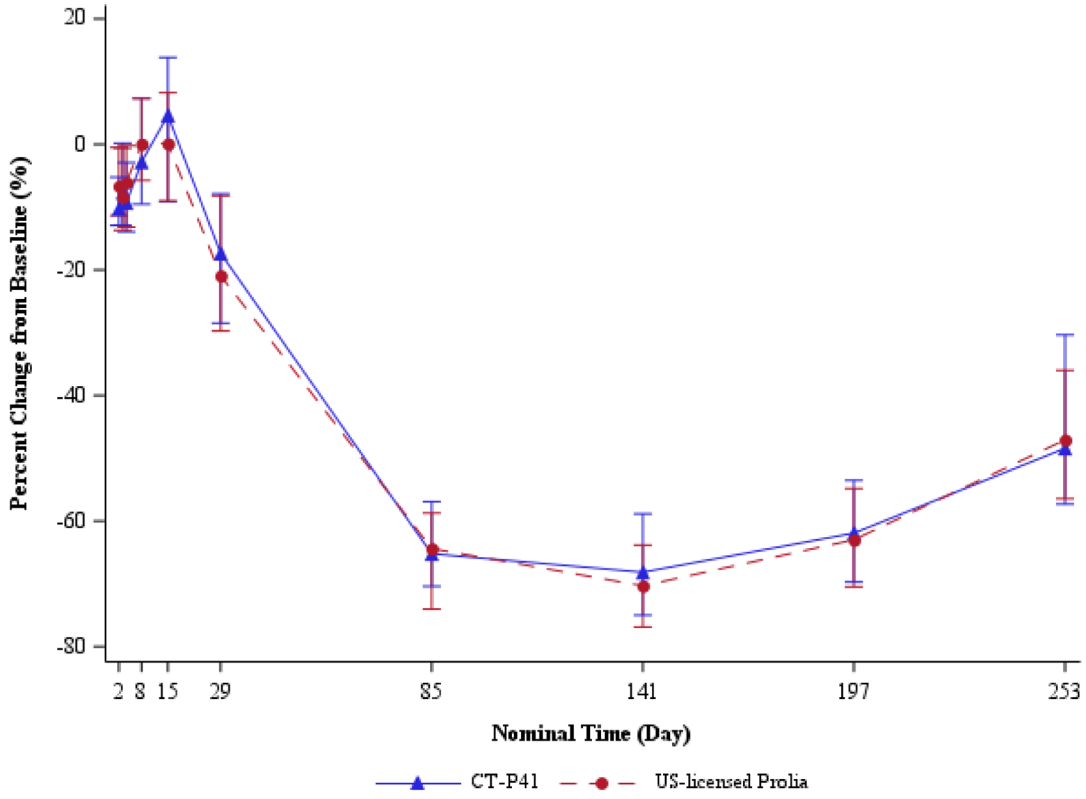
The PD profiles for both markers, s-CTX (**Figure 2**) and P1NP (**Figure 3**), are similar between CT-P41 and US-Prolia.

Figure 2: Median Percent Change from Baseline for Serum Concentration of s-CTX versus Time



Source: Figure 11-2, page 85, Study 1.2, Link to Study 1.2 CSR

Figure 3: Median Percent Change from Baseline for Serum Concentrations of P1NP versus Time



Source: Figure 11-3, page 86, Study 1.2, Link to Study 1.2 CSR

5.3.2 STUDY 3.1

This is a double-blind, randomized, active-controlled, “phase 3” study to compare efficacy, pharmacokinetics, pharmacodynamics, and safety of CT-P41 and US-Prolia in postmenopausal women with osteoporosis. The study was further divided into two treatment periods. In Treatment Period I subjects were randomly assigned 1:1 to CT-P41 or US-Prolia group. At the end of 52 weeks, and beginning of Treatment Period II, subjects initially assigned to US- Prolia in Treatment Period I were randomly assigned again in a ratio of 1:1 to either continue US-Prolia (non-switching arm) or transition to CT-P41 (switching arm). Patients who were initially assigned to CT-P41 in Treatment Period I continued their treatment with CT-P41.

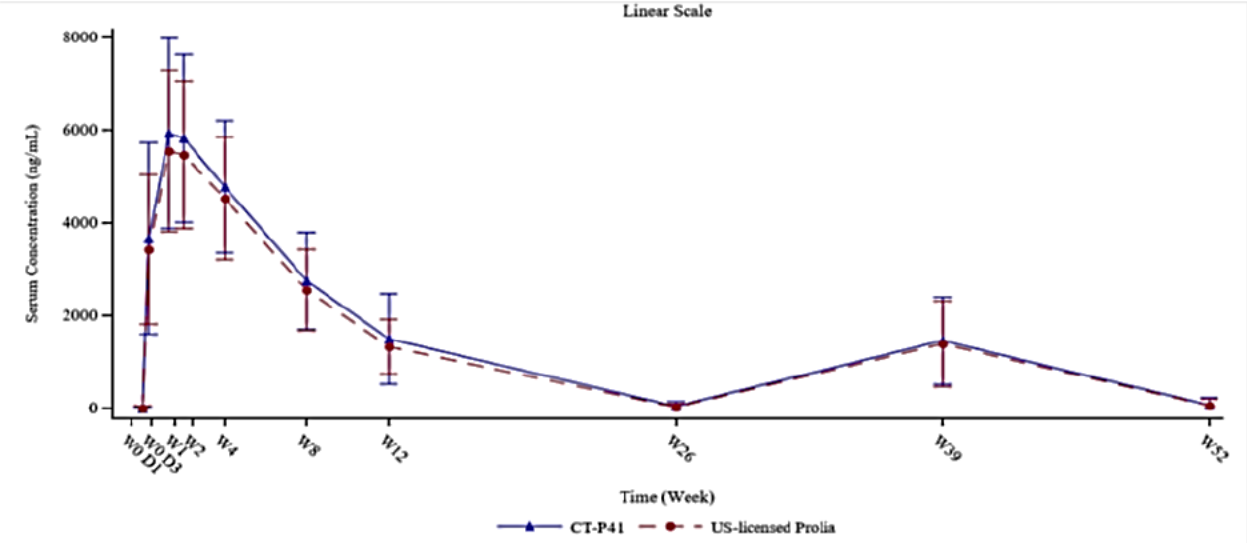
Participants received CT-P41 or US-Prolia as a 60 mg SC injection to the upper arm via PFS on Day 1 (Week 0), Week 26, and Week 52. In addition, all participants received daily supplementation of 1000 mg elemental calcium and at least 400 IU vitamin D. Participants were followed for ~1.5 years (547 days) and at various time points PK, PD,

and immunogenicity were assessed (Refer to Section 6.2 and Appendix 14 (13.2.2.1) for more detailed information on the design of the study).

5.3.2.1 PK Assessment

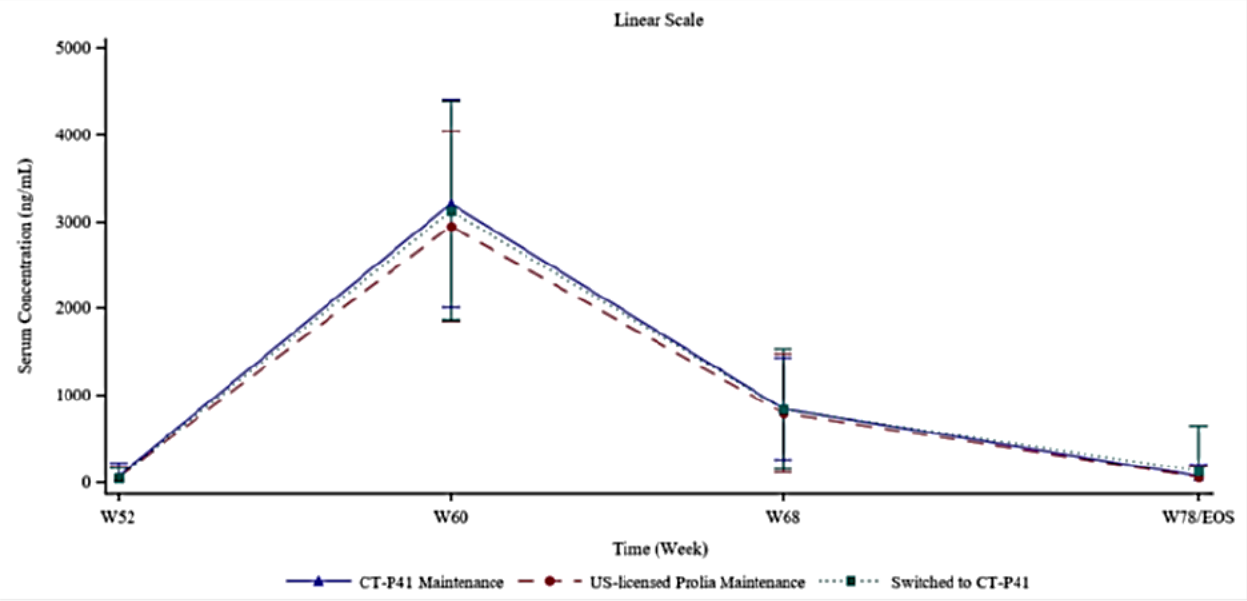
The mean concentration-time profiles are similar between CT-P41 and US-Prolia for Treatment Period 1 (**Figure 4**) and Treatment Period 2 (**Figure 5**).

Figure 4 Mean (±SD) Serum Concentrations of Denosumab in Treatment Period I



Source: Figure 11-1, Page 178; Study 3.1, Link to Study 3.1 CSR

Figure 5 - Mean (±SD) Serum Concentrations of Denosumab in Treatment Period II



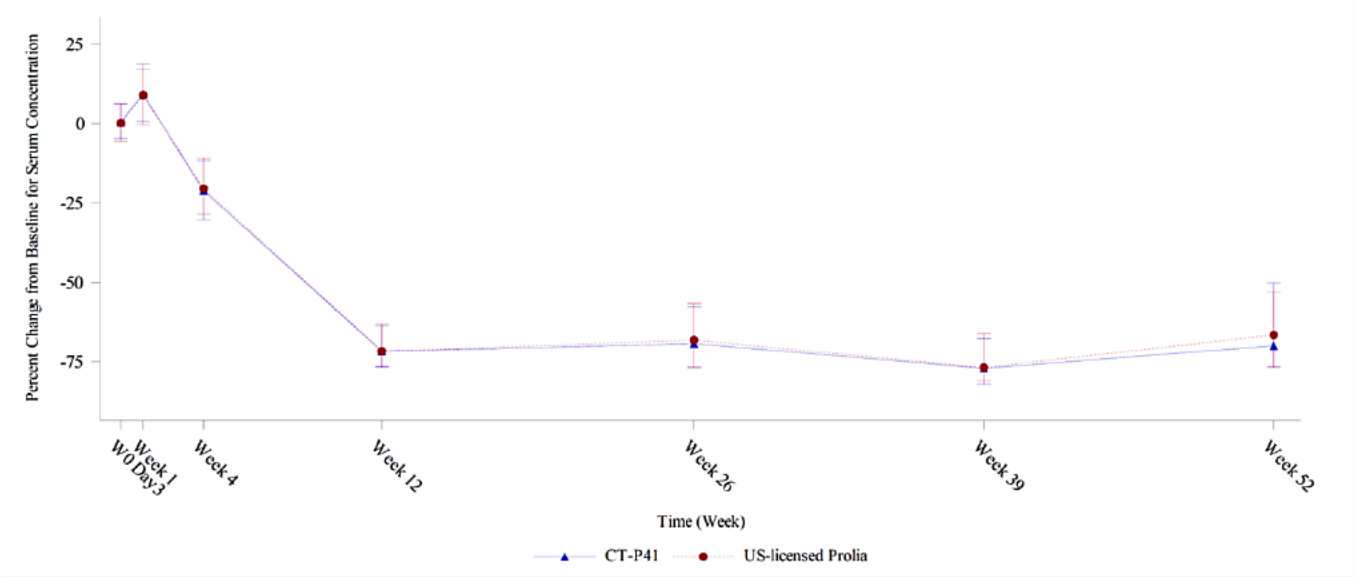
Source: Figure 11-2, page 180, Study 3.1, Link to Study 3.1 CSR

5.3.2.2 PD Assessment

The Applicant collected and analyzed PD data of s-CTX and P1NP in this clinical study. These PD analysis are considered as exploratory and thus results are presented only for completeness.

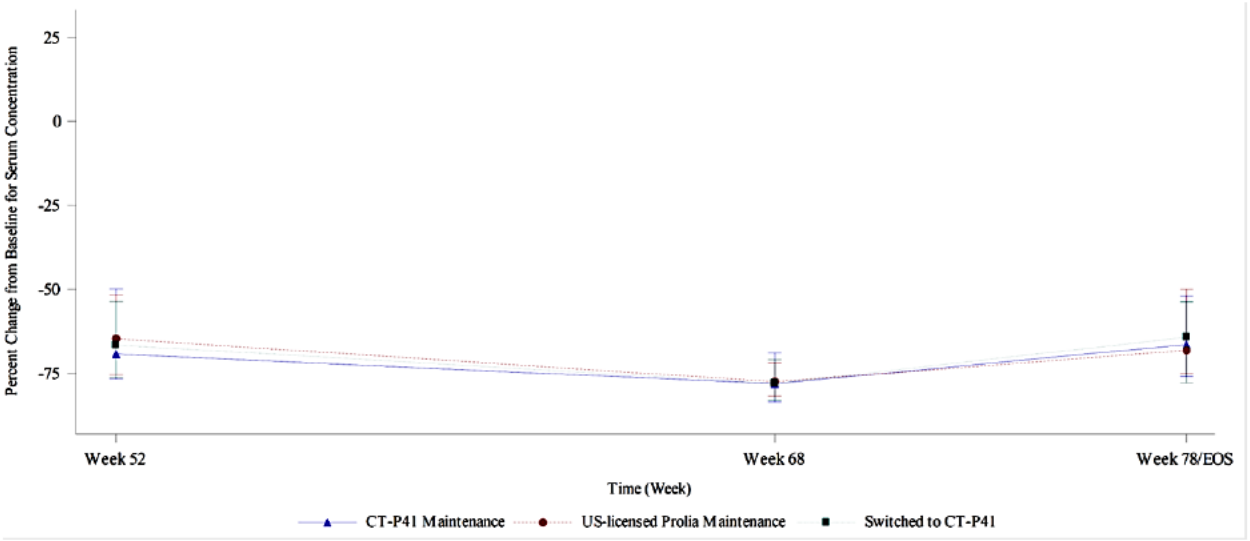
Median percent change from baseline in s-CTX and P1NP for Treatment Period I are shown in **Figure 6** and **Figure 7**, respectively. The PD profiles for both markers are similar for between CT-41 and US-Prolia treatment groups. A similar trend was observed for Treatment Period II (data not shown).

Figure 6 - Median Percent Change from Baseline for Serum Concentration of s-CTX versus Time in Treatment Period I



Source: Figure 11-3, page 185, Study 3.1, Link to Study 3.1 CSR

Figure 7 - Median Percent Change from Baseline for Serum Concentrations of P1NP versus Time in Treatment Period I



Source: Figure 11-6, page 187, Study 3.1 , Link to Study 3.1 CSR

5.4 Clinical Immunogenicity Studies

5.4.1 STUDIES CT-P41 1.2 and CT-P41 3.1

5.4.1.1 Design features of the clinical immunogenicity assessment

Refer to Sections 5.4.1, 6.5, and Appendix 14 (13.2.2.1) for more detailed information on the design of the study.

5.4.1.2 Immunogenicity endpoints

Immunogenicity was a secondary endpoint in Studies 1.2 and 3.1. In these studies, the immunogenicity assessment included incidence of anti-drug antibody (ADA), neutralizing antibody (NAb), and ADA titer levels in the CT-P41 and US-Prolia groups.

5.4.1.2.1 Immunogenicity assay's capability of detecting the ADA and NAb in CT-P41 (the proposed product), and U.S.-licensed Prolia (the reference product) in the study samples

MSD-ECL immunogenicity assay was used to detect ADAs against CT-P41 and US-Prolia. This immunogenicity assay followed a 3-tiered approach consisting of (i) screening assay, (ii) confirmatory assay, and (iii) titration. Initial screening detected "potential positive" ADA samples which were then re-assayed in the confirmatory assay. Samples that were "Positive" for ADAs samples in the confirmatory assay were then further analyzed to detect the presence of NAbs. Those samples that were "Negative" or "N/A" for ADAs in the screening and confirmatory assays were considered as negative

for the presence of ADAs. In the titration phase the “Positive” ADA samples were further analyzed for the presence of NAbs and resulted in a “Positive” or “Negative” signal for the presence of NAb.

Drug tolerance of the ADA/NAb assay is 50,000 ng/mL of CT-P41 or US-Prolia and is much higher than the maximal concentrations of CT-P41 and US-Prolia detected in both studies CT-P41 1.2 and CT-P41 3.1. Thus, it is unlikely that study drug concentrations will interfere with the ADA/NAb assays.

Overall, based on the assessment of bioanalytical method validation, the immunogenicity assays are suitable for the intended purposes for detection of ADA and NAb in collected serum samples (Refer to OPQA3’s review for additional details (Section 3.1))**.**

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

In Study 1.2, ADA samples were collected at pre-dose on Day 1, and Days 2, 3, 4, 8, 15, 29, 57, 85, 141, and 253.

In Study 3.1. ADA samples were collected at on Days 1 (pre-dose), 15, 29, 57, 85, 183 (pre-dose), 274, 365 (pre-dose), 420, 477, and 547 (pre-dose). Samples for immunogenicity testing were collected prior to dosing of the study drug if study drug was administered on the same day visit.

The immunogenicity assessment schedule in Studies 1.2 and 3.1 is acceptable, as it provides a comprehensive assessment of the onset and time course of the ADA response throughout the study duration. In addition, concentrations of the study drug and PD markers were measured when immunogenicity samples were collected to allow for assessment of ADA impact on PK and PD. As maximal serum concentration of study drug in Studies CT-P41 and US-Prolia (<8000 ng/mL) is much lower than the drug tolerance of the ADAs/NAbs assay (~50,000 ng/mL), no interference with the ADAs/NAbs assay in the presence of drug in the serum was expected.

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

The incidence of ADAs and NAbs in the two studies, 1.2 and 3.1, are shown in **Table 9**, **Table 10** and **Table** 11, respectively.

The incidence of ADAs and NAbs was similar between treatment groups for each study. The incidence of NAbs was low in all treatment groups in both studies. Pre-treatment of US-Prolia and transitioning to CT-P41 did not influence the incidence of ADAs and NAbs in CT-P41 group after the transition (Table 11).

Table 9: Immunogenicity results for binding ADA and NAb in Study 1.2

	N	Anti-Drug antibody		NAb
		Baseline	Treatment-Induced	
CT-P41	74	1/74 (1.4%)	74/74 (100%)	2/74 (2.7%)
US-Prolia	77	0/77 (0.0%)	77/77 (100%)	2/77 (2.6%)

Source: Table 12-7, page 104, Study CT-P41 1.2 , Link to Study 1.2 CSR

Table 10: Immunogenicity results for binding ADA and Nab in Study 3.1 from Day 1 to 52 weeks (Treatment period I)

	N	Anti-Drug antibody		NAb
		Baseline	Treatment-Induced	
CT-P41	239	2/239 (0.8%)	233/239 (97.5%)	0/233 (0.0%)
US-Prolia	238	0/238 (0.0%)	234/238 (98.3%)	0/234 (0.0%)

Source: Table 12-29, page 266, Study CT-P41 3.1 , Link to Study 3.1 CSR

Table 11: Immunogenicity results for binding ADA and Nab in Study 3.1 after 52 weeks to 78 weeks (Treatment period II)

	N	Anti-Drug Antibody	NAb
CT-P41/CT-P41	220	194/220 (88.2%)	0/194 (0.0%)
US-Prolia/ US-Prolia	100	87/100 (87.0%)	0/87 (0.0%)
US-Prolia/ CT-P41	101	89/101 (88.1%)	0/89 (0.0%)

Source: Table 12-30 CSR CT-P41 3.1 Pg 268, Link to Study 3.1 CSR

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

Impact of ADA and NAb on PK

Study CT-P41 1.2

The impact of the ADAs on the PK of the drug was compared by analyzing primary PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}) in the CT-P41 and US-Prolia groups by ADA status and titer in study 1.2. For the analyses subjects were stratified into sub-groups with ADA results of negative and positive. The positive titer groups were further stratified into titer bans of 100, 300, or > 900. No formal statistical analysis was conducted. The primary PK parameters $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max} were similar in ADA-positive and ADA-negative subjects, across all treatment groups in study 1.2 (**Table 12**).

Table 12: Impact of ADA Status and Titer on Denosumab PK Parameters in Study 1.2

ADA Result		CT-P41 (n = 74)			US-Prolia (n = 77)			
	n	Mean $AUC_{0\text{-}inf}$ (SD) (day•µg/mL)	$AUC_{0\text{-}last}$ (SD) (day•µg/mL)	C_{max} (SD) (µg/mL)	n	Mean $AUC_{0\text{-}inf}$ (SD) (day•µg/mL)	$AUC_{0\text{-}last}$ (SD) (day•µg/mL)	C_{max} (SD) (µg/mL)
Negative	8	249.09 (77.33)	247.04 (76.82)	5.11 (1.67)	8	180.35 (58.40)	179.56 (58.41)	4.42 (1.31)
Positive	64	343.22 (73.72)	340.74 (73.37)	5.77 (1.33)	67	324.41 (81.21)	320.68 (81.01)	5.74 (1.48)
Titer = 100	37	361.33 (74.67)	358.71 (74.39)	6.03 (1.32)	50	330.04 (78.16)	327.46 (78.17)	5.80 (1.20)
Titer = 300	27	318.40 (65.90)	316.12 (65.51)	5.42 (1.30)	17	307.84 (90.03)	299.50 (88.57)	5.58 (2.14)
Titer ≥ 900	0	-	-	-	0	-	-	-

Source: Table 23, page 36, Integrated Summary of Immunogenicity, Link

Study 3.1

The serum concentrations of CT-P41 and US-Prolia were assessed at T_{max} on Week 2 and around the same time in Week 52 to determine the impact of ADAs on PK. Similar to Study 1.2, the analysis stratified the subjects into subgroups with negative and positive (titer bands 100, 300, or >900) ADA results. No formal statistical analysis was conducted. The serum concentrations for ADA-positive and ADA-negative subjects, have similar values across both groups in study 3.1 (**Table 13**).

Table 13: Impact of ADA Status and Titer on Denosumab Serum Concentration at Week 2 and Week 52 (Treatment Period I) from Study 3.1

Visit	ADA Result	CT-P41 (n = 237)		US-Prolia (n = 236)	
		n	Mean (SD)	n	Mean (SD)
Week 2	Negative	153	6.19 (1.808)	134	5.83 (1.558)
	Positive	71	5.03 (1.557)	90	4.92 (1.463)
	Titer = 100	23	5.05 (1.574)	29	4.93 (1.387)
	Titer = 300	39	4.84 (1.429)	55	4.90 (1.504)
	Titer ≥ 900	9	5.86 (1.933)	6	5.12 (1.688)
Week 52	Negative	140	0.03 (0.088)	128	0.03 (0.134)
	Positive	81	0.16 (0.203)	79	0.12 (0.136)
	Titer = 100	49	0.18 (0.212)	45	0.11 (0.127)
	Titer = 300	31	0.13 (0.190)	30	0.13 (0.156)

Visit	ADA Result	CT-P41 (n = 237)		US-Prolia (n = 236)	
		n	Mean (SD)	n	Mean (SD)
	Titer ≥ 900	1	0.20 (NC)	4	0.09 (0.082)

Source: Table 24, page 37, Integrated Summary of Immunogenicity; NC = not calculated, Link to Integrated Summary of Immunogenicity

5.4.1.5.1 Impact of ADA and NAb on PD

The impact of the ADAs on the primary PD parameters (AUEC of sCTX and AUEC of P1NP) was assessed by comparing the ADA status and titer levels on Day 141 for Study 1.2 (**Table 14**) and Week 52 for Study 3.1(**Table 15**). For the analyses subjects were stratified into sub-groups with ADA results of negative and positive. The positive titer groups were further stratified into titer bans of 100, 300, or > 900. No formal statistical analysis was conducted. The primary PD parameters were similar in ADA-positive and ADA-negative subjects, across all treatment groups in both Studies 1.2 and 3.1.

Table 14: Impact of ADA Status and Titer on PD Parameters in Study 1.2

Visit	ADA Result	CT-P41 (n = 74)		US-Prolia (n = 77)	
		n	Mean (SD)	n	Mean (SD)
AUEC of s-CTX (day*% inhibition)	Negative	8	16867.67 (3973.194)	8	15755.35 (2561.060)
	Positive	63	19603.08 (1974.035)	66	19342.99 (1870.274)
	Titer = 100	37	20102.02 (1673.006)	50	19717.28 (1640.406)
	Titer = 300	26	18893.03 (2177.346)	16	18173.31 (2107.358)
	Titer ≥ 900	0	-	0	-
AUEC of P1NP (day*% inhibition)	Negative	8	9964.40 (3454.196)	8	11245.83 (2624.279)
	Positive	63	12654.87 (2819.086)	66	13013.31 (2107.617)
	Titer = 100	37	12802.33 (3337.319)	50	13451.75 (1841.024)
	Titer = 300	26	12445.02 (1895.495)	16	11643.20 (2352.409)
	Titer ≥ 900	0	-	0	-

Source: Table 25, page 36, Integrated Summary of Immunogenicity, Link to Integrated Summary of Immunogenicity

Table 15: Impact of ADA Status and Titer on PD Parameters (Treatment Period I) from Study 3.1

Visit	ADA Result	CT-P41 (n = 237)		US-Prolia (n = 236)	
		n	Mean (SD)	n	Mean (SD)
AUEC of s-CTX (day*% inhibition)	Negative	140	14210.78 (3010.741)	128	14508.85 (2184.868)
	Positive	81	15269.01 (2601.969)	79	15506.98 (2096.348)
	Titer = 100	49	15338.06 (2551.122)	45	15706.02 (1576.293)
	Titer = 300	31	15133.92 (2755.466)	30	15095.65 (2775.146)
	Titer ≥ 900	1	16073.61 (NC)	4	16352.82 (363.372)
AUEC of P1NP (day*% inhibition)	Negative	140	8873.61 (2610.169)	128	9026.59 (2334.022)
	Positive	81	9665.61 (2610.851)	79	9776.17 (1980.103)
	Titer = 100	49	9718.09 (2835.317)	45	10117.00 (1384.907)
	Titer = 300	31	9600.88 (2301.203)	30	9265.29 (2643.358)
	Titer ≥ 900	1	9100.28 (NC)	4	9773.37 (1383.490)

Source: Table 26, page 39, Integrated Summary of Immunogenicity, Link to Integrated Summary of Immunogenicity

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5.4.1.5.2 Impact of ADA and NAb on Safety

Study 1.2
All subjects in each of the two treatment groups had at least one post-treatment positive ADA during the study. Neutralizing antibody positivity incidence was the same in both

groups, occurring in 2.7% (2/72) and 2.6% (2/73) of subjects in the CT-P41 and US-Prolia treatment groups, respectively. There were no treatment-emergent adverse events classified as drug-related hypersensitivity/allergic reaction in Study CT-P41 1.2.

Study 3.1

Treatment Period 1

The incidence of positive ADA at any time during treatment period 1 was 98% in both CT-P41 (N=234/239) and US-Prolia (N=234/238) treatment groups. Of the patients with positive ADA results, no patients in the 2 groups were positive for NAb.The high rate of ADA positivity precluded a determination of antibody presence alone on specific adverse events during treatment.

When examining adverse events in subjects who developed the highest titers of ADA (i.e., >900) at any time during treatment period 1, there was no meaningful difference in the frequency or nature of most common treatment emergent adverse events compared to the entire study population receiving the same treatment (see Table 16).

Table 16. Most common treatment emergent adverse events (i.e., incidence >5%) in patients with ADA titer >900 compared to entire study population, Treatment Period 1, Study 3.1

	CT-P41		US-Prolia	
	Titer ≥900 (N=72)	entire dataset (N=239)	Titer ≥900 (N=59)	Entire dataset (N=238)
COVID-19	10 (14)	28 (12)	7 (12)	26 (11)
URI	10 (14)	25 (11)	2 (4)	20 (8)
Arthralgia	7 (10)	24 (10)	4 (7)	21 (9)
Nasopharyngitis	5 (7)	10 (4)	3 (5)	12 (5)

Source: clinical reviewer analysis

Treatment Period 2

During the second treatment period, ADA positivity continued to be high as shown in Table 17. The percentage of subjects with ADA titers >900 was highest in the CT-P41 transition group (Table 17). No subject in any treatment group developed neutralizing antibodies during treatment period 2.

Table 17. Incidence of ADA positive results and incidence of ADA titer >900 during treatment period 2, Study 3.1

	CT-P41 maintenance (N=220)	US-Prolia maintenance (N=100)	CT-P41 switch (N=101)
	Number (%) of Patients		
ADA Positive during treatment	194 (88)	87 (87)	89 (88)
Titer >900	19 (9)	7 (7)	12 (12)

No subject's antibody titer remained at 900 or above by the end of study visit.

Among subjects with ADA antibody titers >900 during treatment period 2, there were no injection site reactions reported. The sample size of subjects with high titers was too small to make a meaningful comparison of TEAEs compared to the overall treatment group.

Of the four subjects with injection site reaction documented during treatment period 2, one subject, in the CT-P41 maintenance group, had detectable ADA titer (in this case, titer of 100) at the time of injection site reaction. The other three did not have detectable titer coinciding with occurrence of injection site reaction.

Overall, there does not appear that development of anti-drug antibodies had a meaningful impact on safety, and there was no clinically meaningful difference between treatment groups in occurrence of immunogenicity.

5.4.1.5.3 Impact of ADA and NAb on Efficacy

To assess the potential impact of anti-drug antibodies on efficacy in study 3.1, the Applicant analyzed percent change from baseline in LS BMD at Week 52 stratified by ADA status and titer. Results, shown in Table 18, were numerically similar regardless of antibody status or titer. Overall, the development of anti-drug antibodies does not appear have a meaningful impact on efficacy.

The results of the comparative immunogenicity assessment support the demonstration that CT-P41 has no clinically meaningful differences from US-Prolia and US-Xgeva.

Table 18. Percent Change from baseline in LS BMD at week 52 according to ADA status and titer, study 3.1, full analysis set

ADA Result	CT-P41 (N=239)		US-Prolia (N=238)	
	n	Mean (SD)	n	Mean (SD)
Negative	138	5.17 (3.886)	127	5.56 (3.966)
Positive	81	6.19 (3.530)	79	6.18 (3.231)
Titer = 100	49	6.48 (3.458)	45	6.04 (3.230)
Titer = 300	31	5.74 (3.705)	30	6.39 (3.313)
Titer ≥ 900	1	5.64 (NC)	4	6.29 (3.413)

Source: BLA 761404 SD 1, module 5.3.5.3.ISI, Table 27, p. 40

6 Statistical and Clinical Evaluation and Recommendations

6.1 Statistical and Clinical Executive Summary and Recommendation

In the single comparative clinical study in post-menopausal women with osteoporosis (Study CT-P41 3.1), the demographic and baseline disease characteristics of the two treatment groups (US-Prolia and CT-P41) were similar. The primary efficacy endpoint was the mean percentage change from baseline to Week 52 in lumbar spine (LS) bone mineral density (BMD) assessed by DXA scan. At Week 52, the difference in the mean percentage change from baseline in LS-BMD between CT-P41 and US-Prolia was 0.19 with the 90% confidence interval between -0.86 and 0.3, which was contained within the pre-defined equivalence margin of +/-1.45%. Therefore, this study demonstrated that there is no clinically meaningful difference between the two products with respect to efficacy. There was also no meaningful difference between CT-P41 and US-Prolia with respect to the nature or frequency of treatment emergent adverse events.

At Week 52, subjects in the CT-P41 treatment group received a final dose of CT-P41 while those assigned to US-Prolia were re-randomized in a 1:1 ratio to receive a final dose of CT-P41 or US-Prolia. Subjects were followed for six months after this final dose of study drug. At six months (Week 78), LS BMD was re-assessed by DXA. there was no clinically meaningful difference in mean percent change from baseline in LS BMD among the three treatment groups (see Table 25). There was also no increase in the nature or frequency of adverse events, or immunogenic response. Data for this single transition supports that administration of CT-P41 following US-Prolia does not present clinically meaningful differences in efficacy or safety as compared to remaining on US-Prolia.

6.1.1 Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical analyses.

6.2 Review of Comparative Clinical Studies with Statistical Endpoints:

Study CT-P41 3.1: A double-blind, randomized, active-controlled, “Phase 3” study to compare efficacy, pharmacokinetics, pharmacodynamics, and safety of CT-P41 and US-licensed Prolia in Postmenopausal women with osteoporosis

6.2.1 Data and Analysis Quality

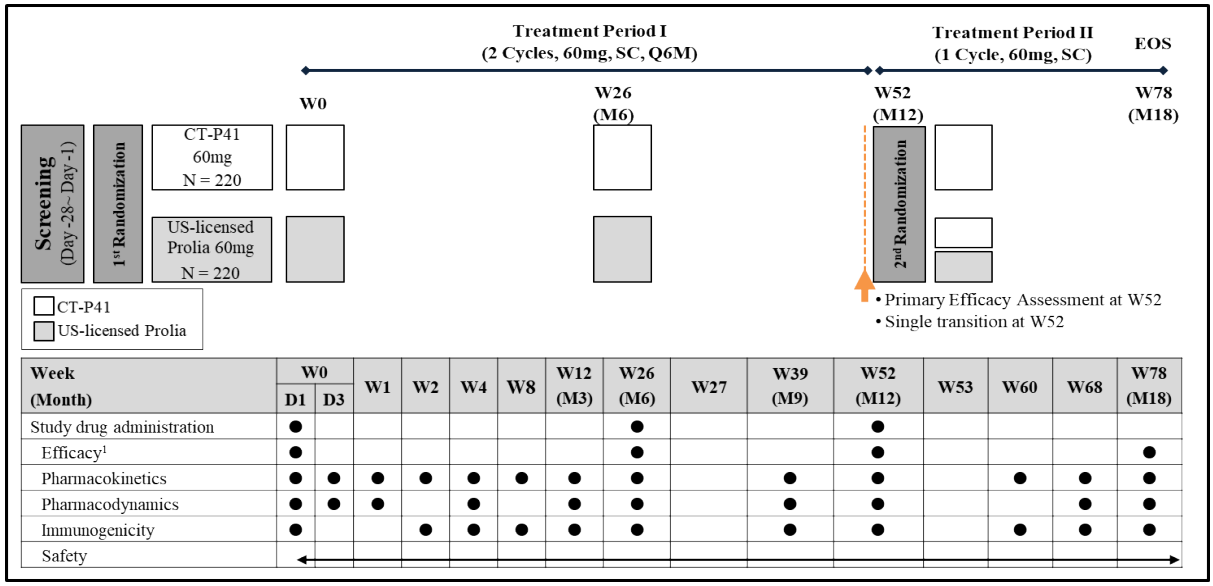
There are no concerns regarding data quality and integrity.

6.2.2 Study Design and Endpoints

Study CT-P41 3.1 was an international, multicenter, randomized, double-blind study, consisting of two treatment periods. For the first treatment period (i.e., TP1), a total of 479 female subjects with post-menopausal osteoporosis (PMO) were randomized in a 1:1 ratio to receive two doses of either CT-P41 60 mg or US-Prolia 60 mg on Day 1 and at Week 26. Randomized was stratified by age (<65 years and ≥65 years), baseline lumbar spine (LS) BMD T-score (≤-3.0 and >-0.3) and prior bisphosphonate therapy (Yes or No).

At Week 52, treatment period 2 (TP2) commenced. All subjects in the CT-P41 group continued treatment with a third dose of CT-P41 60 mg SC. Subjects who had received US-Prolia during TP1 were re-randomized in a 1:1 ratio to either continue on US-Prolia 60 mg SC or switch to CT-P41 60 mg SC. Subjects were followed for an additional 26 weeks. The study design is shown in Figure 8.

Figure 8. CT-P41 3.1 Study Design



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	◄														►

Source: BLA 761404 SD 1, module 5.3.5.1, CT-P41 3.1 clinical study report, Figure 9-1, p. 47

To qualify for study participation, subjects had to be post-menopausal, aged 50 to 80 years and have osteoporosis according to bone mineral density (BMD) criteria on DXA scan (absolute lumbar spine BMD T-score < -2.5 and > -4.0). Subjects also had to be naïve to denosumab. Use of medications with bone effects, or presence of underlying conditions that could impact bone quality or density were additional exclusion criteria. Refer to section 0 for complete list of entry criteria.

CT-P41 or US-Prolia were administered by unblinded study staff, and the SC injection was administered in the upper arm, upper thigh or abdomen. The dose used in the study is the same as the dose of US-Prolia indicated for treatment of postmenopausal osteoporosis [i.e. 60 mg injected subcutaneously (SC) every 6 months].

All subjects also received at least 1000 mg of elemental calcium and 400 IU vitamin D daily, with adjustment made as necessary based on results of calcium and serum 25 (OH) vitamin D levels during treatment

The primary efficacy endpoint of percent change from baseline in BMD for lumbar spine (L1 to L4) was measured at Week 52. The same DXA instrument was to be used for all study procedures for an individual patient. If the same scanner was no longer available, the study site followed the central imaging provider's guidance on selecting an appropriate replacement scanner and a phantom scanning process to quantify any calibration differences. All DXA scans were submitted to and analyzed by a central imaging vendor.

Secondary efficacy endpoints were not controlled for type-1 error.

The study duration was 78 weeks and the protocol required 16 visits to the study clinic. DXA scan was performed at screening and again at treatment weeks 26, 52 and 78. Safety assessments included vital sign measurement, immunogenicity sampling (for anti-drug and neutralizing antibodies) and hematology serum chemistry testing at regular intervals. Injection site reactions were assessed 30 minutes after the end of administration of study drug. The complete schedule of assessments is shown in **Table 45**.

6.2.3 Statistical Methodologies

Analysis Population

The intent-to-treat (ITT) population in treatment period 1 was defined as all randomized subjects regardless of the study drug being administered or not. The full analysis set (FAS) was defined as all subjects who receive at least 1 full dose of the study drug. The primary efficacy analysis was performed using the full analysis set. There was a total of 479 subjects in the ITT population, 240 subjects in the CT-P41 group and 239 subjects in the US-licensed Prolia group. However, the FAS included 477 (99.6%) subjects (239 [99.6%] and 238 [99.6%] subjects in the CT-P41 and US-licensed Prolia groups, respectively). Two subjects, one from each treatment group, were excluded from the FAS due to these subjects not meeting the inclusion or exclusion criteria who were randomly assigned to study drug by site staff's mistake and then were terminated from the study before the initiation of the study treatment. Using the FAS population appears acceptable as long as all subjects who were randomized and received at least one dose of the study treatment, regardless of whether they have post-baseline efficacy measurement are included in the analysis.

Primary Efficacy Analysis

The Applicant's prespecified primary analysis of the primary endpoint, the percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52, was performed using an analysis of covariance (ANCOVA) model with missing values imputed using multiple imputation, assuming missing at random (MAR). The model

included treatment as a fixed effect and age, baseline BMD T-score at the lumbar spine, and prior bisphosphonates therapy (Yes versus No) as covariates. A margin of ± 1.45% was used to determine clinical similarity. If the 90% confidence interval (CI) of the difference in the mean of the primary efficacy endpoint between treatment groups falls entirely within the similarity margin, (−1.45%, 1.45%), then comparative effectiveness between the test and reference products will be declared.

Missing data

For the primary analysis using the ANCOVA model, if the Week 52 BMD lumbar spine was missing, the corresponding value of the percent change from baseline was imputed assuming missing at random.

There were about 10% missing data at Week 52 (7% in the CT-P41 group and 11% in the US-Prolia group). The Applicant conducted some sensitivity analyses to evaluate the impact of missing data on the analysis conclusion for the primary endpoint. A 2-dimensional tipping point analysis was conducted with a gradual shift in imputed values in each treatment group until the 90% CI was no longer entirely within the therapeutic similarity margin of ±1.45%. They also conducted an analysis on the primary endpoint, using two one-sided tests with missing data multiply imputed under the corresponding null. One test included subtracting the imputed values for the CT-P41 group by the similarity margin to test non-inferiority. The other test included adding the imputed values for the CT-P41 group by the margin to test non-superiority. In both tests, missing values in the reference group was assumed to be MAR. In agreement with FDA, this method was only applied to the subjects outside Ukraine in CT-P41 treatment group considering missing data were primarily due to the war. For subjects in Ukraine, the imputed values were not adjusted so the initial imputed values remain the same.

Secondary endpoints

The secondary endpoints were as follows:

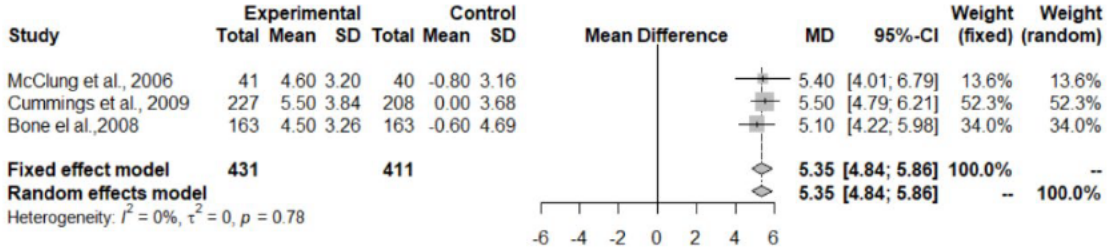
- Percent change from baseline in BMD for lumbar spine (L1 to L4), total hip, and femoral neck by DXA at Weeks 26 and 52
- The incidences of new vertebral, nonvertebral, and hip fractures during the study
- Change from baseline in health-related quality of life at Weeks 26 and 52.

All the secondary endpoints were summarized using descriptive statistics or frequency tables. There were no multiplicity adjustments made for the secondary endpoints.

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

The similarity margin, which was agreed upon by FDA, was based on three published clinical trials (see **Table 9**).

Figure 9. Meta-analysis of treatment effects of denosumab - placebo



Source: Figure 2, Summary of Clinical Efficacy, Study CT-P41, pages 10-12.

Based on this meta-analysis, the point estimate of the difference in treatment effects is 5.35% with 95% CI (4.84%, 5.86%). The Applicant stated that the lower bound of the 95% CI is used to justify an appropriate margin:

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

There were no significant modifications to the protocol that would affect interpretation of study results.

6.2.4 Subject Disposition

The majority of subjects completed both Treatment Periods 1 and 2 (see Table 19 and Table 20). The intent-to-treat set included all patients randomized to receive study drug regardless of whether any study drug was administered. The most common reason for premature discontinuation was voluntary patient withdrawal.

Table 19. Subject disposition, Study CT-P41 3.1, Treatment Period 1

	CT-P41 N(%)	US-Prolia N(%)
Treatment Period 1		
Randomized (ITT Set)	240 (100)	239 (100)
Completed	221 (92)	201 (84)
Discontinued prematurely	18 (8)	37 (16)
Withdrawal by patient	8 (3)	24 (10)
Adverse event	4 (2)	5 (2)
Significant protocol violation	5 (2)	4 (2)
Investigator decision	1 (<1)	0
Disease progression	0	1 (<1)

Source: BLA 761404 SD 1, module 5.3.5.1, CT-P41 3.1 clinical study report, Table 10-1

During treatment period 2, a single subject assigned to CT-P41 maintenance discontinued study treatment due to an adverse event that began during treatment period 1. This subject never received study drug in treatment period 2 but did remain in the study and completed all follow-up assessments. Table 20 shows patient disposition for Treatment Period 2.

Table 20. Subject disposition, Study CT-P41 3.1, Treatment Period 2

	CT-P41 maintenance (N=221)	US-Prolia maintenance (N=100)	Switch to CT-P41 (N=101)
	N(%)	N(%)	N(%)
Randomized	221	100 (100)	101 (100)
Initiated study treatment	220 (99)	100 (100)	101 (100)
Discontinued study treatment during treatment period II	1 (<1)	0	0
Completed study treatment	220 (99)	100 (100)	100 (100)

Source: BLA 761404 SD 1 module 5.3.5.1.Study CT-P41 3.1, 14 Tables and Figures Referred to but not included in the Text, Table 14.1.2.

The nature of adverse events leading to study discontinuation are discussed in section 6.4.5.

6.2.5 Demographics and Baseline Characteristics

The demographics and baseline disease characteristics (see Table 21 and Table 22) were balanced between the treatment groups. Majority of subjects were aged 65 years or older and had never smoked. All were white. Median BMI suggests a normal weight population.

Table 21 Demographic Characteristics, Study CT-P41 3.1

Demographic variable	**CT-P41 (N=240)**	**US-Prolia (N=239)**
Age		
Mean (SD) years	66 (6.3)	66 (6.6)
<65 years	101 (42)	101 (42)
>/=65 years	139 (58)	138 (58)
Race		
White	240 (100)	239 (100)
Median BMI (kg/m2)	24	25

Demographic variable	CT-P41 (N=240)	US-Prolia (N=239)
Smoking Status		
Never	163 (68)	162 (68)
Former	33 (14)	33 (14)
current	44 (18)	44 (18)

Source: clinical reviewer analysis

The majority of subjects had never used bisphosphonates. Approximately one-quarter of subjects in both groups had a vertebral fracture present on baseline lateral spine x-ray. A slight excess of subjects in the US-Prolia group had a history of non-vertebral fracture compared to incidence in the CT-P41 group (39% versus 31%, respectively). Baseline BMD T-score category was split evenly between ≤-3.0 and >-3.0. A BMD T-score of ≤-2.5 and ≥-4.0 was required for study enrollment.

Table 22 Baseline Disease Characteristics, Study CT-P41 3.1

	CT-P41 (N=240)	US-Prolia (N=264)
Prior bisphosphonate use		
Yes	32 (13)	28 (12)
No	208 (87)	211 (88)
Fracture History		
Vertebral fracture present at baseline	59 (25)	50 (21)
h/o non-vertebral fx	75 (31)	93 (39)
Baseline LS BMD (T-score) category		
≤ -3.0	120 (50)	120 (50)
>-3.0	120 (50)	119 (50)

Source: BLA 761404 SD 1 module 5.3.5.1.Study CT-P41 3.1, 14 Tables and Figures Referred to but not included in the Text, Table 14.1.4
<LLN = less than the lower limit of normal

6.2.6 Analysis of Primary Clinical Endpoint(s)

This study met the primary efficacy endpoint given the 90% CI for the difference between CT-P41 and US-Prolia was contained within the pre-specified margin of (-1.45%, 1.45%). The Applicant's primary efficacy results were confirmed by the statistical review team. The primary analysis results for LS-BMD at Week 52 is shown in Table 23 with missing data imputed assuming MAR.

Table 23. Primary Analysis: Percent Change from Baseline in BMD for Lumbar Spine by DXA at Week 52, Full Analysis Set, Study CT-P41 3.1

	CT-P41 N=239	US-Prolia N=238
Baseline mean BMD for lumbar spine	0.75 (0.07)	0.74 (0.06)

	CT-P41 N=239	US-Prolia N=238
LS Means (SE)	4.96 (0.3)	5.15 (0.3)
Treatment difference (CT-P41 - Prolia)	-0.19	
90% CI	-0.76, 0.38	

Source: Statistical Reviewer's Analysis; adsl.xpt, addxa.xpt
[1] Primary objective met if the 90% CI for the difference between CT-P41 and US-Prolia was contained within the pre-specified margin of (-1.45%, 1.45%).
Note: LS Means are from the analysis of covariance with treatment (CT-P41, US-Prolia), treatment as a fixed effect and age, baseline BMD T-score at the lumbar spine, and prior bisphosphonates therapy (Yes versus No) as covariates. Multiple imputation under the MAR assumption was performed for missing data imputation.
Note: The treatment mean difference was calculated as CT-P41 - US-Prolia.
Abbreviations: CI, confidence interval; LS, least squares; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; N, total number of subjects; SD, standard deviation; SE, standard error

6.2.7 Potential Effects of Missing Data

Results from the two pre-specified sensitivity analyses are shown below. Table 24 shows the results from two one-sided tests with missing data imputed under the corresponding null, one test for non-inferiority and the other test for non-superiority. This method was applied only to the subjects outside of the Ukraine in the CT-P41 treatment group. Results from the two tests support the conclusion of similarity.

Table 24. Sensitivity Analysis: Percent Change in Baseline in BMD for Lumbar Spine by DXA at Week 52, FAS Multiple Imputation adjusted for Ukraine, Study CT-P41 3.1

	CT-P41 N=239	US-Prolia N=238
Baseline mean BMD lumbar spine (SD)	0.75 (0.07)	0.74 (0.06)
Multiple imputation #1[1]		
LS Means (SE)	4.89 (0.3)	5.13 (0.3)
Treatment difference (CTP41-Prolia)	-0.25	
90% CI[2]	-0.82, 0.32	
Multiple imputation #2[1]		
LS Means (SE)	5.03 (0.3)	5.17 (0.3)
Treatment difference (CTP41-Prolia)	-0.14	
90% CI[2]	-0.71, 0.43	

Source: Statistical Reviewer's Analysis; adsl.xpt, addxa.xpt
[1]Imputation #1: Subtract the imputed values by the margin, 1.45, to test non-inferiority
Imputation #2: Add the imputed values by the margin, 1.45, to test non-superiority.
For patients outside Ukraine in CT-P41 group, the imputed values were adjusted by the non-inferiority or non-superiority margin (±1.45) assuming each null hypothesis was true. For the others, the imputed values were not adjusted so the initial imputed values remained the same.

[2] Primary objective met if the 90% CI for the difference between CT-P41 and US-Prolia was contained within the pre-specified margin of (-1.45%, 1.45%).
Note: LS Means are from the analysis of covariance model with treatment (CT-P41, US-Prolia), age, baseline BMD T-score of the lumbar spine, and prior bisphosphonate therapy (yes, no)
Note: The treatment mean difference was calculated as CTP41 – US Prolia.
Abbreviations: CI, confidence interval; LS, least squares; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; N, total number of subjects; SD, standard deviation; SE, standard error

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

6.2.8 Analysis of Secondary Clinical Endpoint(s)

6.2.8.1 LS-BMD at week 78

Although not controlled for type I error or subject to hypothesis testing, LS BMD values were assessed by DXA at Week 78, coinciding with six months after the single transition dose. The mean percent change from baseline in lumbar spine BMD at week 78 was similar among the three treatment groups, varying at most by 0.4% (see Table 25).

Table 25. Mean (SD) Percent Change from baseline to week 78 in LS BMD, study 3.1

	CT-P41 maintenance (N=220)	US-Prolia Maintenance (N=100)	Transition to CT-P41 (N=101)
Mean (SD)	6.8 (4)	6.6 (3)	7.0 (4)

Source: BLA 761404 SD 1, module 5.3.5.1, CT-P41 3.1 clinical study report, Table 11-11

6.2.8.2 Fractures

Study 3.1

Incidence of non-traumatic new vertebral (from T4 to L4), nonvertebral (excluding skull, facial bones, mandible, metacarpals, metatarsals and phalanges) and hip fractures was a protocol specified secondary endpoint. Though not controlled for type I error, these data inform the overall safety profile of CT-P41.

Lateral spine X-ray was performed at screening and at weeks 26, 52 and 78. Images were read centrally and vertebral fracture, if present, was graded using the Genant scale. A new vertebral fracture was defined as an increase of at least one grade in any vertebra from T4 to L4 that had been normal at Screening. Only fractures confirmed by the central imaging vendor were to be included for the efficacy analysis.

Treatment Period 1

The number of subjects experiencing new vertebral and nonvertebral fractures was similar in both treatment groups.

Table 26. Incidence of new vertebral, nonvertebral and hip fracture,

Treatment Period 1, CT-P41 3.1

	CT-P41	US-Prolia
New vertebral fracture	1 (0.4)	1 (0.4)
New nonvetebral fracture	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	0	0

Source: clinical reviewer analysis

Treatment Period 2
During treatment period 2, two patients in the CT-P41 maintenance group experienced nonvertebral fracture (radius distal, in both patients). There were no non-vertebral in the other treatment groups. Hip fracture and vertebral fracture were not reported in any treatment group during treatment period 2.

These data do not suggest a clinically meaningful difference between CT-P41 and US-Prolia in the incidence of non-traumatic vertebral and non-vertebrtal fracture, nor an increased risk of fracture following transition from US-Prolia to CT-P41.

6.3 Review of Safety Data

6.3.1 Methods

The evaluation of safety is based primarily on the comparative clinical study in post-menopausal women with osteoporosis (study 3.1). However, safety data from the single-dose PK similarity study (study 1.2), which enrolled healthy adult males, was also examined for known risks of CT-P41 (e.g., hypersensitivity reactions, hypocalcemia) and to further evaluate any new safety signals that become apparent during review of the post-menopausal osteoporosis (PMO) data.

Safety analysis was performed on the safety set which included all patients who received at least one dose of study drug.

The size of the safety database is adequate to make a determination of clinical comparable safety between CT-P41 and US-Prolia.

6.3.2 Categorization of Adverse Events

In both study 1.2 and 3.1, a treatment emergent adverse event (TEAE) was defined as any event not present before exposure to study drug or worsening of an existing event after exposure to study drug.

Abnormal results of diagnostic procedures including laboratory test abnormalities were considered AEs if they fulfilled the following:

- Resulted in discontinuation from the study
- Required treatment or any other therapeutic intervention
- Required further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- Were clinically significant as evaluated by the investigator

Disease progression of postmenopausal osteoporosis was not recorded as an adverse event.

Adverse events were coded to system organ class and preferred term according to Medical Dictionary for Regulatory Activities version 26.0 and severity graded according to the Common Terminology Criteria for Adverse Events Version 5.0.

6.3.3 Safety Analyses

Safety data were not combined because the study populations and designs differed.

Study 3.1 consisted of two treatment periods – the first comparing CT-P41 and US-Prolia and the second period designed to evaluate the safety of a transition from US-Prolia to CT-P41 compared to continuing on US-Prolia. Safety data from the two treatment periods are presented separately.

6.3.4 Major Safety Results

6.4.4.1 Relevant Characteristics of the Population Evaluated for Safety

Study 1.2 enrolled healthy adult male volunteers, who do not reflect the population for whom study drugs is indicated. Nonetheless the population was considered appropriate and sensitive given the primary objectives of the study.

Study 3.1 enrolled post-menopausal women with osteoporosis which is one of the target populations for study drugs. Demographic and baseline disease characteristics of the study population are shown in Table 21.

6.4.4.2 Deaths

Study 1.2
No deaths occurred in comparative PK study 1.2.

Study 3.1
In study 3.1 there were two deaths, both in subjects receiving CT-P31.

- A 63-year old white female (patient ID (b) (6) died from progression of ovarian cancer. Cancer was diagnosed during treatment period II at an

unspecified date following receipt of third CT-P41 injection and death occurred approximately six weeks following diagnosis. There was no further information on this patient's risk factors, if any, for ovarian cancer. Death was deemed unrelated to study drug.

- A 79-year old white female (patient ID (b) (6) with a past medical history of diabetes mellitus, coronary artery disease (CAD), congestive heart failure and hypertension died from exacerbation of coronary artery disease. Death occurred 324 days after the Week 0 dose of CT-P41. Death was considered related to prior history of CAD and risk factors for CAD, and unrelated to study drug.

6.4.4.3 Serious Adverse Events

Study 1.1
No serious treatment emergent adverse events (TEAEs) occurred in the study.

Study 3.1

Treatment Period 1
During treatment period I, eight serious TEAEs occurred in 7 (3%) subjects in the CT-P41 group and 13 SAEs occurred in 10 (4%) subjects in the US-Prolia, respectively. No preferred term was reported more than once. System organ class in which SAE's occurred are shown Table 27. Preferred terms occurring in the CT-P41 group were *diverticulum intestinal*; *gastric disorder*; *large intestinal*

Table 27. Serious Adverse Events by SOC, Treatment Period 1, Study 3.1

	CT-P41 (N=239)	**US-Prolia (N=238)**
SOC	N(%)	N(%)
Any serious AE	7 (3)	10 (4)
Cardiac disorders	1 (<1)	1
Gastrointestinal disorders	1 (<1)	2
Infections and infestations	0	1
Injury, poisoning and procedural complications	0	2
Musculoskeletal and connective tissue disorders	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2
Nervous system disorders	0	1
Reproductive system and breast disorders	0	1
Respiratory, thoracic and mediastinal disorders	0	1
Vascular disorders	1	0

Treatment Period 2
During treatment period 2, serious TEAE's occurred in 8 (4%), 2 (2%) and 0 subjects in the CT-P41 maintenance, US-Prolia maintenance and switch to CT-P41 groups,

respectively. Unstable angina occurred in two CT-P41 maintenance subjects. Otherwise, no preferred term were reported in more than one subject.

There was no meaningful difference in either the nature or frequency of serious TEAE's between CT-P41 and US-Prolia or following a switch from US-Prolia to CT-P41 compared to US Prolia maintenance.

6.4.4.4 Treatment Emergent Adverse Events

Study 1.2

In the comparative PK study the nature of treatment emergent adverse events was similar between the two treatment groups. The incidences of these events differed to some degree, but the disparity is likely due to chance and does not reflect differences in product safety. The most common TEAEs (i.e., those occurring in >3% of subjects) are shown in Table 28. Treatment-emergent adverse events in >3% subjects

Table 28. Treatment-emergent adverse events in >3% subjects, Study CT-P41 1.2

	CT-P41 (N=74)	US-Prolia (N=77)
	N(%)	N(%)
Blood calcium decreased	28 (38)	35 (46)
COVID-19	8 (11)	7 (9)
Nasopharyngitis	6 (8)	8 (10)
ALT increased	6 (8)	4 (5)
LDL increased	3 (4)	6 (8)
Coronavirus infection	2 (3)	6 (8)
AST increased	3 (4)	2 (3)
Arthralgia	3 (4)	2 (3)
Blood bilirubin increased	1 (1)	3 (4)
Paresthesia	3 (4)	0
Blood CPK increased	3 (4)	0

Source: BLA 761404 SD 1, module 5.3.5.1, CT-P41 3.1 clinical study report Table 12-3, p. 93.

The preferred term *blood calcium decreased* is notably high in both groups. 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; however, supplementation was not required nor furnished by the study facility. Adverse events of hypocalcemia (blood calcium decreased) are discussed in 6.4.7.1.

Study 3.1

Treatment Period 1

The nature of adverse events was similar between treatment groups and consistent with the known safety profile of study drugs. Small numeric differences in actual incidence (for example, UTI) between groups is likely due to chance rather than inherent differences in study drug. The most common TEAEs (i.e., occurring in >3% of subjects) are shown in Table 29.

Table 29. Most Common Treatment Emergent Adverse Events, Treatment Period 1, Study 3.1, Safety Population

	CT-P41 (N=239)	**Prolia (N=238)**
	N(%)	N(%)
Any TEAE	181 (76)	167 (70)
Covid-19	28 (12)	26 (11)
Arthralgia	24 (10)	21 (9)
URI	25 (11)	20 (8)
Vitamin D deficiency	15 (6)	6 (3)
UTI	12 (5)	5 (2)
Osteoarthritis	10 (4)	13 (6)
Nasopharyngitis	10 (4)	13 (5)
Constipation	7 (3)	9 (4)
hypercalcemia	8 (3)	7 (3)
Headache	6 (3)	11 (5)
Back pain	6 (3)	8 (3)
Hypocalcemia	6 (3)	7 (3)
Hypercholesterolemia	6 (3)	7 (3)

Source: clinical reviewer analysis

*Percentages rounded to nearest whole number

For reference, in the placebo-controlled phase 3 trial for the PMO indication, treatment emergent adverse events occurring in >5% of subjects and more frequently in Prolia compared to placebo were *back pain*, *pain in extremity*, *hypercholesterolemia*, *musculoskeletal pain* and *cystitis*. This pattern is consistent with events reported in study 3.1.

Treatment Period 2

In treatment period 2, subjects transitioning from US-Prolia to CT-P41 experienced a greater incidence of adverse events than those subjects who were maintained on US-Prolia or CT-P41. This difference was largely driven by a higher rate of *URI* (*preferred term)* in the transition group (see Table 30).

Table 30. Most Common Treatment Emergent Adverse Events, Treatment Period 2, Study 3.1, Safety Population

	US-Prolia/ CT-P41	CT-P41/ CT-P41	US-Prolia/ US-Prolia
N (%)	101 (100)	220 (100)	100 (100)
Any TEAE	54 (54)	107 (49)	41 (41)
URI	11 (11)	13 (6)	4 (4)
COVID-19	6 (6)	8 (4)	3 (3)
nasopharyngitis	4 (4)	4 (2)	3 (3)
Vitamin D deficiency	4 (4)	6 (3)	3 (3)
Arthralgia	1 (1)	7 (3)	0
Blood parathyroid hormone increased	0	0	3 (3)

Source: BLA 761404 SD 1, module 5.3.5.1, CT-P41 3.1 clinical study report, Table 12-7.

Although the incidence of URI was greater in the transition group, it is notable that the event rates in the two maintenance groups were very similar. URI is a labeled adverse reaction for US-Prolia and occurred in 4.9% of Prolia treated subjects in the PMO registration trial. The excess incidence of URI reports following the transition from US-Prolia to CT-P41 neither represents a meaningful safety difference between the two products, nor is an unacceptable risk of transition.

6.4.5 Dropouts and/or Discontinuations

The protocols had a general requirement to discontinue study drug for an adverse event that would compromise patient safety. In addition, in study 3.1, worsening of osteoporosis, defined below, would necessitate discussion of study drug discontinuation and alternative treatment:

- ≥7% decrease in LS or TH BMD at month 12 compared to baseline
- Decrease in BMD T-score below -4.0 at LS or TH
- Osteoporosis related fracture (e.g., vertebral compression fracture or hip fracture)

There were otherwise no provisions for discontinuation in the event of a specific adverse event.

Study 1.2
No subject discontinued prematurely due to an adverse event.

Study 3.1
Treatment Period 1

Five subjects each in the CT-P41 [5/239 (2.1%)] and US-Prolia [5/238 (2.1%)] groups discontinued treatment early due to adverse events. No single preferred term was cited more than once as a reason for discontinuation (see Table 31). Only the event of osteonecrosis of the jaw, which occurred in a US-Prolia treated subject, was considered drug related.

Table 31. Treatment Emergent Adverse Events Leading to Study Drug Discontinuation, Treatment Period 1, Study 3.1

	CT-P41 (N=239)	US-Prolia (N=238)
	N (%) of Patients	
Total number of subjects discontinuing due to an adverse event /AE Preferred Term	5 (2)	5 (2)
Cataract	0	1 (<1)
Crohn's disease	1 (<1)	0
Toothache	1 (<1)	0
Respiratory tract infection	1 (<1)	0
Alanine aminotransferase increased	0	1 (<1)
Hepatic enzyme increased	1 (<1)	0
Osteonecrosis of the jaw	0	1
Basal cell carcinoma	0	1
Borderline ovarian tumor	0	1 (<1)
Pancreatic carcinoma	1 (<1)	0

Source: BLA 761404 SD 1, module 5.3.5.1, CT-P41 3.1 clinical study report Table 12-12, p. 229

One (1/238, <1%) subject assigned to US-Prolia discontinued early for osteoporosis disease progression. However, this event was not coded as a discontinuation due to an adverse event in the study report.

Treatment Period 2
During Treatment Period 2, a single subject assigned to the CT-P41 maintenance group discontinued early due to hepatic transaminase enzyme elevation that began during treatment period 1. Transaminase levels did not exceed three times the upper limit of normal (ULN) and were not associated with increased bilirubin. Study drug was stopped but the subject remained in the study. Transaminase values subsequently returned to normal. The cause of the transient transaminase elevation was not identified in the study report.

There were no withdrawals due to osteoporosis disease progression.

6.4.6 Additional Safety Evaluations

6.4.6.1 Laboratory Findings

6.4.6.1.1 Calcium and Minerals
Denosumab can cause hypocalcemia and disturbances in bone-related mineral levels (i.e., reduced phosphorous and magnesium). The US-Prolia prescribing information advises that calcium, phosphorous and magnesium be monitored within 14 days of injection, as the nadir for serum calcium occurs within the first two weeks following administration of denosumab.

Abnormal labs were graded for severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE toxicity grading scale for hypomagnesemia, hypocalcemia, and hypophosphatemia is shown in Table 32. Toxicity for derangements in magnesium and calcium are based on laboratory values. For phosphorous, toxicity is graded based on clinical symptoms and requirement for intervention rather than on specific laboratory findings.

Table 32. CTCAE Toxicity Grading Scale for Hypomagnesemia, Hypocalcemia and Hypophosphatemia [3]

	Toxicity Grade				
	1	**2**	**3**	**4**	**5**
Hypomagnesemia (nl range 0.65-1.05 mmol/L)	<LLN-0.5	0.4-<0.5	0.3-<0.4	<0.3	death
Hypocalcemia (normal 2.12-2.62 mmol/L)	2.0-<LLN	1.75 - <2.0	1.5-<1.75	<1.5	death
Hypophosphatemia	No intervention indicated	Noninvasive intervention indicated	Severe/ medically significant but not immediately life-threatening; hospitalization indicated	Life-threatening consequences; urgent intervention indicated (e.g., dialysis)	Death

Study CT-P41 1.2

Subjects could take daily supplementation of vitamin D at a dose of 400 IU to 1000 IU (inclusive) at the discretion of the investigator to reduce risk of hypocalcemia and vitamin D deficiency, but this supplementation was not required.

Clinical laboratory tests (chemistry, hematology, urinalysis) were obtained at screening and one day prior to dosing, and again post-injection days 3 and 8, and weeks 2, 4, 8, 12, 20 and 28.

[3] US Department of Health and Human Services. (Nov. 27, 2017). Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Retrieved October 22, 2024, from chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf

The incidence of hypocalcemia within the first two weeks following study drug injection, which coincides with the anticipated calcium nadir following denosumab injection, was high in both treatment groups but numerically higher in the US-Prolia group compared to CT-P41 (Table 33). All hypocalcemia cases were CTCAE grade 1 with the exception of three CT-P41 patients with grade 2 abnormalities (values of 1.97 mmol/L in each of the three patients).

Table 33. N (%) of subjects experiencing shift in serum calcium from normal at baseline to less than the lower limit of normal (<LLN) during the 14-day period after study drug injection (i.e., at post-injection days 3, 8 and 15) Study CT-P41 1.2

	CT-P41 n(%) N=74 (100)	US-Prolia n(%) N=77 (100)
Serum Ca++ transition from normal at baseline to <LLN	29 (39)	37 (48)

Source: clinical reviewer analysis

Although the percentages of subjects experiencing values of serum calcium below the lower level of normal is high, the fact that this incidence is fairly balanced between the two treatment groups is reassuring and suggests that the calcium derangements were exacerbated by subjects' underlying nutritional status and lack of required calcium and vitamin D supplementation.

Treatment emergent adverse events of hypocalcemia were also high in this study and balanced between groups, occurring in 28 (38%) and 35 (46%) of subjects in the CT-P41 and US-Prolia groups, respectively (refer to Table 28). There were no protocol specified criteria for classifying a low calcium laboratory value as an adverse event and this was at the discretion of the investigator.

Study CT-P41 3.1

Unlike study 1.2 where supplementation was discretionary, all patients in the comparative clinical study were to receive daily supplementation containing at least 1,000 mg of elemental calcium and at least 400 IU vitamin D from randomization to end-of-study (EOS) visit in order to prevent hypocalcemia.

Treatment Period 1

During treatment period I, safety laboratory testing (hematology, serum chemistry including serum calcium and 25-OH vitamin D) occurred at screening and at Day 1 and Weeks 1, 4, 12 and 26 following injection of study drug. Additional measurement of serum 25-OH vitamin D, albumin-adjusted total serum calcium, and serum calcium, phosphate and magnesium occurred prior to study drug injection at Week 26 (corresponding to the second study drug injections) and was analyzed at a local laboratory.

The Applicant's assessment window only captures the first week of the 2-week period during which calcium nadir is anticipated after study drug injection. The Clinical Study Report presented results for both serum calcium and albumin-corrected serum calcium. As approximately 40% of total body calcium is protein bound, serum calcium may be artificially low in the setting of hypoalbuminemia. In those situations, a correction formula to account for the low albumin is used to estimate actual levels of biologically active calcium (i.e., ionized calcium).[4] Correction is not necessary in patients with normal serum albumin.

Patients were required to have an albumin-adjusted total serum calcium ≥8.5 mg/dL (≥2.125 mmol/L) at screening. Albumin was below the lower limit of normal in eight subjects at some point during the trial but only slightly, and at time points not concurrent with occurrence of hypocalcemia. Therefore, this review focuses on serum calcium rather than on albumin-corrected serum calcium

Incidences of laboratory hypocalcemia, hypomagnesemia and hypophosphatemia were low during the week following the first and second study drug administrations and were balanced between treatment groups (see Table 34).

Table 34, N (%) of subjects with shift in serum Ca++ , Magnesium and Phosphorous to below the lower limit of normal (<LLN) in first week after study drug administration, Treatment Period 1, Study 3.1

		CT-P41 (N=239) N(%)	US-Prolia (N=238) N(%)
<LLN			
calcium	Week 1	2 (0.8)	1 (0.4)
	week 27	0	0
magnesium	Week 1	1 (0.4)	0
	Week 27	0	0
phosphorous	Week 1	4 (1.7)	4 (1.7)
	Week 27	5 (2.1)	2 (<1)

Source: clinical reviewer's analysis

Treatment Period 2

Treatment period 2 commenced at the Week 52 study visit when subjects received their third and final dose of study drug and the single transition from US-Prolia to CT-P41 was evaluated. Serum calcium was assessed at week 53 -- one week after study drug injection.

[4] Kenny CM, Murphy CE, Boyce DS, Ashley DM, Jahanmir J. Things We Do for No Reason™: Calculating a "Corrected Calcium" Level. J Hosp Med. 2021 Aug;16(8):499-501.

As shown in Table 35, the incidence of calcium, magnesium and phosphorous values below the lower limit of normal was low in all groups and at a comparable incidence. All hypocalcemic values were categorized as Grade 1 toxicity with the exception of one case meeting Grade 2 criteria (Ca of 1.99 mmol/L [normal 2.18- 2.6]) in a subject in the CT-P41 maintenance group.

Table 35 Number(%) of subjects with serum calcium, magnesium and phosphorous transition from normal at baseline to <LLN one week after study drug injection, Treatment Period 2

	CT-P41maintenance N=220	US Prolia maintenance N=100	Switch to CT-P41 N=101
<LLN			
Serum calcium	4 (1.8)	1 (1)	3 (3)
Serum magnesium	1 (<1)	1 (1)	1 (1)
Serum phosphorous	2 (<1)	0	1 (1)

Source: clinical reviewer analysis

6.4.6.1.2 Other Laboratory Tests

During treatment period 1, clinical laboratory tests (chemistry, hematology, urinalysis) were obtained at screening and one day prior to dosing, and again on post-injection days 3 and 8, and at weeks 2, 4, 8, 12, 20 and 28. During treatment period 2, the same labs were repeated at week 52, prior to dosing, and at weeks 1, 16 and 26 post-injection. There were no meaningful differences between treatment groups in median change in chemistry or hematology parameters over time during Treatment Period 1 or 2.

Because of the discontinuation due to elevated transaminase values that occurred in a subject assigned to CT-P41 during Treatment Period 1, the incidence of shifts in liver function tests from normal to above normal during treatment was examined.

Treatment Period 1

During treatment period 1, a single patient in the CT-P41 group experienced transient elevation in serum ALT and AST >3X ULN without concomitant elevation in total bilirubin. One subject in the US-Prolia group had an ALT >3X ULN that was not associated with other liver function test abnormalities (see Table 36).

	CTP-P41 N=239 N(%)	US-Prolia N=238 N(%)
ALT		
>3X ULN	1 (<1)	1 (<1)
AST		
>3X ULN	1 (<1)	0
Total bilirubin		

	CTP-P41 N=239 N(%)	US-Prolia N=238 N(%)
>2X ULN	0	0

Table 36. Incidence of LFT transitioning from normal at baseline to above normal during treatment, Treatment Period 1, Study 3.1

	CTP-P41 N=239 N(%)	US-Prolia N=238 N(%)
ALT		
>3X ULN	1 (<1)	1 (<1)
AST		
>3X ULN	1 (<1)	0
Total bilirubin		
>2X ULN	0	0

Source: Clinical reviewer's analysis

Treatment Period 2

There were no patients with new shifts in liver function tests from normal at baseline to high during TP2. Two patients who experienced transamination elevation during TP1 continued to have such elevation during TP2 but values had normalized by the week 78/end of study visit.

6.4.7 Adverse events of Special Interest

6.4.7.1 Injection Site Reactions/Local Site Pain immediately following study drug administration

In both the comparative PK study and the comparative clinical study, injection site reactions were assessed 30 minutes (±10 minutes) after study drug administration and severity of any reaction graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. (see Figure 10).

Figure 10. Injection site reaction score (CTCAE grading)

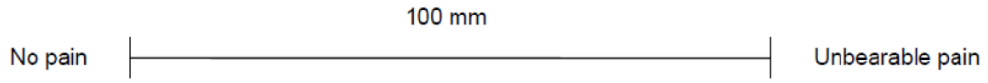
None	0	No reaction
Mild	1	Easily tolerated erythema and/or light bruising and/or mild pain
Moderate	2	Disturbing erythema with swelling and/or disturbing bruising and/or disturbing pain
Severe	3	Almost intolerable symptoms, or clinically definite skin necrosis, characterized by any of the following: oozing, weeping, skin breakdown, ulceration, scar formation

Source: internal source document

Study 1.2
Study drug was administered to the outer upper arm area on the subject's non-dominant side.

Local site pain was assessed using a 100 mm visual analogue scale (VAS) immediately (within 15 minutes) after study drug administration (Day 1). Subjects were asked to indicate their current level of pain intensity by drawing a single vertical line (|) on the 100 mm line (see Figure 11 Figure 11**).**

Figure 11. Visual Analogue Scale



Source: internal source document

Median VAS result (mm) was 1.00 in both treatment groups. Range was 0 mm to38 mm in CT-P41 and 0mm to 36.0 mm in the US-Prolia group.

Two (2.7%) subjects in the CT-P41 group experienced grade 1 injection site reaction compared to none in the US-Prolia group.

Study 3.1
Treatment Period 1
Injection site reactions were documented following study drug administration in five (2%) of CT-P41 subjects and 3 (1%) of US-Prolia subject. All events were categorized as

CTCAE grade 1 except for one grade 2 event which occurred in a CT-P41 treated subject.

Treatment Period 2
During treatment period 2, there were three individuals (1%) with grade 1 injection site reactions in the CT-P41 maintenance group and one subject (1%) with grade 1 reaction in the CT-P41 transition group. No reactions were reported in the US-Prolia maintenance group.

There was a slight excess of injection site reactions occurring in both comparative studies in CT-P41 treated subjects. However, the reactions were mild (maximum severity of grade 2 in one subject) and this difference compared to US-Prolia is not considered to be clinically meaningful.

6.4.7.2 Hypersensitivity/Allergic Reaction
Hypersensitivity reaction was a protocol specified adverse event of special interest in both clinical studies.

Study 1.2
There were no TEAEs classified as drug-related hypersensitivity reactions in either treatment group.

Subjects' vital signs were monitored pre-dose and at pre-specified intervals post-dose (30 minutes, and 1, 3, 6 and 12 hours) for indications of possible hypersensitivity reaction. There was no meaningful difference between the treatment groups in change in any vital sign parameter during the 12 hour period after dosing.

Study 3.1
Monitoring of vital signs as an early indication of a hypersensitivity reaction occurred prior to study administration and again at 1 hour after injection on Day 1, week 26 and week 52.

Treatment Period 1
During treatment period 1, there was no meaningful difference between the treatment groups in incidence of abnormal vital signs (i.e., decrease or increase in blood pressure, heart rate; increased respiratory rate or temperature) one hour after dosing. There were also no meaningful changes in individual parameters compared to pre-dose in either treatment group.

The safety dataset was searched for adverse event preferred terms coding to the Hypersensitivity Reaction FDA Medra Query (FMQ). Of the cases identified, the following were excluded:

- one report of *dermatitis allergic* caused by mosquito bite
- two case of *dermatitis allergic* which were not temporally related to study drug injection (occurring 58 days and 79 days, respectively, after study drug injection)

- one report of *hypersensitivity* which was attributed to inhaled allergy and occurred prior to dosing
- two cases of *eosinophilia* which occurred 78 days and 94 days, respectively, after last dose of study drug. Though eosinophilia can occur with delayed type IV hypersensaitivy reactions, there would typically be other clihical symptoms which were not present in these patients.
- One report of *drug hypersensitivity* which was attributed to ibuprofen

The remaining TEAEs coding to the hypersensitivity FMQ are displayed in Table 37 which shows a similar incidence of such events between treatment groups.

All injection site reactions with a CTCAE score ≥1 were coded as adverse events.

Table 37. TEAEs adjudicated as representing possible study drug-related hypersensitivity, Treatment Period 1, Study CT-P41 3.1

	CT-P41 N=239	US-Prolia N=238
Hypersensitivity FMQ	7 (3)	6 (3)
Injection site reaction	5 (2)	3 (1)
Urticaria	1 (<1)	1 (<1)
Hypersensitivity	1 (<1)	2 (<1)

Source: clinical reviewer analysis

Treatment Period 2

During treatment period 2 at Week 52, there was no meaningful difference between the treatment groups in incidence of abnormal vital signs (i.e., decrease or increase in blood pressure, heart rate; increased respiratory rate or temperature) one hour after dosing compared to immediately prior to dosing.

This reviewer searched the safety dataset for adverse event preferred terms coding to the Hypersensitivity Reaction FDA Medra Query (FMQ). Of the events identified in treatment period 2, the following were excluded:

- Two reports of *eosinophilia* were identified at routine blood draw on first day of treatment period 2 (simultaneous with study drug injection)
- One case of *eosinophilia* occurred 180 days after treatment period 2 study drug injection without associated symptoms
- One case of *Skin reaction* occurred secondary to an insect bite
- *Angioedema* occurred on study day 460, 95 days after study drug injection
- One case of *hypersensitivity* was due to inhalant allergy and occurred 25 days after study drug injection.

After the cases above were excluded, the incidence of hypersensitivity AEs was similar in the treatment groups, with injection site reaction being most common (See Table 38).

Table 38. TEAEs adjudicated as representing possible study drug-related hypersensitivity, Treatment Period 2, Study CT-P41 3.1

	CT-P41maintenance N=220	US Prolia maintenance N=100	Switch to CT-P41 N=101
Hypersensitivity FMQ	4 (2)	0	1 (<1)
Injection site reaction	3 (1)	0	1 (<1)
Hypersensitivity	1 (<1)	0	0

6.5 Clinical Conclusions on Immunogenicity

The assessment of immunogenicity occurred in the comparative pharmacokinetic study 1.2 and the comparative clinical study 3.1. There was no meaningful difference between the treatment arms in either study with respect to development of anti-drug antibodies (ADAs) or neutralizing antibodies (NAbs). Furthermore, presence of ADAs or Nabs had no apparent impact on efficacy or safety outcomes. Refer to Section 5.4 for complete details of the immunogenicity assessment and conclusions from the Clinical Pharmacology review team.

Authors:

Olivia Easley
Clinical Reviewer

Shivangi Vachhani
Clinical Team Leader

(b) (4)

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(b) (4)

7 Labeling Recommendations

7.1 Nonproprietary Name

The Applicant's proposed nonproprietary name, denosumab-bmwo, was found to be conditionally accepted by the Agency.[5]

[5] Nonproprietary Name Suffix Advice Letter filed to BLA 761404, finalized August 13, 2024.

7.2 Proprietary Name

The proposed proprietary names for CT-P41 are conditionally approved as "STOBOCLO" (for denosumab-bmwo 60 mg/mL) and "OSENVELT" (for denosumab-bmwo 120 mg/1.7 mL). These names have been reviewed by DMEPA, who concluded the names were acceptable.[6]

7.3 Other Labeling Recommendations

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

FDA requested a safety labeling change (SLC) on November 7, 2023, for US-Prolia (BLA 125320) following completion of a newly identified safety signal (NISS) assessment of the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD) treated with denosumab.[7] In the NISS assessment, FDA concluded that denosumab has been shown to substantially increase the risk of severe and potentially fatal hypocalcemia compared to oral bisphosphonates in dialysis dependent and advanced CKD patients, and that current labeling is insufficient to convey this risk. The SLC called for the changes to the Prolia labeling. Changes were made to the proposed Prescribing Information for Stoboclo to align with the Prescribing Information for US-Prolia (see Table 39).

A summary of changes to the draft labeling for Stoboclo and Osenvelt are included in Table 39 and Table 40, respectively.

Table 39: Summary of major changes made to the Stoboclo Prescribing Information

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized STOBOCLO Prescribing Information
All Sections	Updated text throughout the Full Prescribing Information to align with Prolia and language used when referring to a denosumab biosimilar. 'Stoboclo,' 'denosumab,' or 'denosumab products' were used in place of Prolia as applicable.
BOXED WARNING	Added a Boxed Warning for severe hypocalcemia in patients with advanced kidney disease to align with Prolia Prescribing Information (S-213; approved March 5, 2024)

[6] Proprietary Name Granted Letters filed to BLA 761404, finalized February 28, 2024.
[7] NISS Integrated Safety Assessment ID 1004972 of BLA 125320 finalized in DARRTS on Oct 20, 2023.

2 DOSAGE AND ADMINISTRATION	**2.1 Information Essential to Safe Dosing or Administration** • Subheading title changed to "Pregnancy Testing prior to Initiation of Stoboclo" to reflect the recommendation to rule out pregnancy prior to administration of Stoboclo. 2.4 **Preparation and Administration** We revised to the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit." per 21 CFR 201.57(c)(3)(iv).
5 WARNINGS AND PRECAUTIONS	**5.2 Drug Products with Same Active Ingredient** • Section edited to state "Patients receiving Stoboclo should not receive other denosumab products concomitantly" to identify "denosumab products", which includes Prolia, Stoboclo, and any other denosumab biosimilar.
6 ADVERSE REACTIONS	• Updated "Hypocalcemia" to "Severe Hypocalcemia and Mineral Metabolism Changes" to align with the update warning for severe hypocalcemia • Removed "(b) (4) because contact information for reporting adverse reactions is included in Highlights. **6.1 Clinical Trials Experience** • Added " The most common adverse reactions reported with denosumab in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis" to align with Prolia labeling. • Updated Table 1 - listing adverse reactions by frequency, (b) (4) to show the most prominent adverse reactions first. **6.3 Immunogenicity** • Relocated immunogenicity information to subsection 12.6, per Immunogenicity in labeling guidance
8 SPECIFIC POPULATIONS	**8.4 Pediatric Use** • Added "In one multicenter, open-label study with denosumab conducted in 153 pediatric patients with

	osteogenesis imperfecta, aged 2 to 17 years, evaluating fracture risk reduction, efficacy was not established." • Added "Clinical studies in pediatric patients with osteogenesis imperfecta were terminated early due to the occurrence of life-threatening events and hospitalizations due to hypercalcemia." • The additions are aligned with Prolia, which summarized the terminated pediatric studies submitted to Prolia (S-213; approved 3/4/2024). The safety and effectiveness of Prolia (denosumab) were not established in pediatric patients; therefore, a summary of studies and any differences in adverse reactions should be included in subsection 8.4 Pediatrics Use per the Pediatric Labeling Guidance. **8.7 Hepatic Impairment** • Deleted subsection 8.7 Hepatic Impairment because it is not a required subsection and should not be included unless sufficient data are available concerning the use of the drug in other specified subpopulations.
10 OVERDOSAGE	Deleted section 10. The section should not be included in labeling if there are no overdosage information. The applicant confirmed there is no experience with overdosage of STOBOCLO.
12 CLINICAL PHARMACOLOGY	**12.3 Pharmacokinetics** • Included major subheadings Absorption, Distribution, and Elimination, per the Clinical Pharmacology Labeling Guidance. **12.6 Immunogenicity** • Updated per the Labeling for Biosimilar (b) (4) Products, Revision 1 (September 2023). • Relocated immunogenicity information from subsection 6.3 • Added new introductory statement "The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of denosumab or of other denosumab products." This provides important background and context to the information provided in the immunogenicity subsection. • Updated the summary of antidrug antibody effect

17 PATIENT COUNSELING INFORMATION	Drug Products with Same Active Ingredient Section revised to "Advise patients that if they receive Stoboclo, they should not receive other denosumab products concomitantly *[see Warnings and Precautions (5.2)]*."
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	**3 Dosage Forms and Strengths** • Added description of the drug product – clear, colorless to pale yellow solution **11 Description** • Reordered inactive ingredients **16 How Supplied/Storage and Handling** • Added description of the drug product – clear, colorless to pale yellow solution • Added "to protect from light" to provide rationale for store in original carton

Table 40: Summary of major changes made to the Osenvelt Prescribing Information

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized OSENVELT Prescribing Information
All Sections	Updated text throughout the Full Prescribing Information to align with Xgeva and language used when referring to a denosumab biosimilar. 'OSENVELT,' 'denosumab,' or 'denosumab products' were used in place of Prolia as applicable.
2 DOSAGE AND ADMINISTRATION	**2.1 Important Administration Instructions** • Added "Osenvelt should be administered by a healthcare provider" to provide specific direction for the administration of this product (see 21 CFR 201.57(c)(3)(iv)).[8] 2.5 **Preparation and Administration** • Revised to the verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, [redacted (b) (4)]." per 21 CFR 201.57(c)(3)(iv). • Deleted [redacted (b) (4)] " from product description. [redacted (b) (4)], this is an inaccurate

[8] Separately, a prior approval supplement request letter was sent to Amgen identifying that a statement should be added in Section 2.1 of the Xgeva (denosumab) Prescribing Information and carton and container labeling that the product should be administered by a healthcare provider. See DARRTS for BLA 125320.

	description of Osenvelt. The Osenvelt solution is essentially free of visible particles based on the specifications, per quality team.
5 WARNINGS AND PRECAUTIONS	**5.2 Drug Products with Same Active Ingredient** • Section edited to state "Patients receiving Osenvelt should not receive other denosumab products concomitantly" to identify "denosumab products", which includes Xgeva, Osenvelt, and any other denosumab biosimilar.
6 ADVERSE REACTIONS	**6.3 Immunogenicity** • Added standard language "The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of denosumab or of other denosumab products", which provides important background and context to the information provided in the immunogenicity subsection.
17 PATIENT COUNSELING INFORMATION	Drug Products with Same Active Ingredient Section revised to "Advise patients (b) (4) Osenvelt (b) (4) they should not receive other denosumab products concomitantly *[see Warnings and Precautions (5.1)]*."
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	**3 Dosage Forms and Strengths** • Added description of the drug product – clear, colorless to pale yellow solution **11 Description** • Added route of administration • Reordered inactive ingredients **16 How Supplied/Storage and Handling** • Added description of the drug product – clear, colorless to pale yellow solution • Osenvelt strength is 120 mg/1.7 mL. To provide product strength per mL, package type term, and container closure, "(70 mg/mL) in a single-dose vial" was added. • Added "to protect from light" to provide rationale for store in original carton

Authors:

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Associate Director for Labeling

Shivangi Vacchani, MD
Cross Discipline Team Leader

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

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

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 13.1 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

Authors:

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Clinical Reviewer, DGE

Shivangi Vachhani, MD
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

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

Author:

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Clinical Reviewer, DGE

10 Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment

to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a "new active ingredient" for purposes of PREA.

At the time of this review, other denosumab products, Jubbonti and Wyost, have been approved as interchangeable biosimilars and have qualified for FIE. CT-P41 will be approved as a biosimilar product, as discussed in section 1.7, and therefore is considered to have a new active ingredient for the purposes of PREA. The Applicant submitted the initial Pediatric Study Plan (iPSP) on July 29, 2022, and an agreement letter was issued on December 21, 2022.

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

Prolia:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture,
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture,
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer,
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer, and
- Treatment of glucocorticoid-induced osteoporosis in pediatric patients <5 years of age at high risk for fracture.

Xgeva:

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

The applicant submitted a pediatric assessment for giant cell tumor of the bone that is unresectable or where surgical resection is likely to result in severe morbidity in skeletally mature adolescents based on a demonstration of biosimilarity and providing adequate scientific justification to support extrapolation of data and information to support licensure. Refer to section 6.7 for review of the assessment.

US-Prolia has a PREA post-marketing requirement (PMR) to conduct a study to evaluate

the safety and efficacy of denosumab in pediatric patients aged 5-17 years old with glucocorticoid-induced osteoporosis (final report submission date: May 2024). A PREA PMR is required for the assessment of CT-P41 for the treatment of glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age and can be deferred until the pediatric data from US-Prolia becomes available.

PeRC discussed this application on October 15, 2024, and concurred with the Division's recommendations.

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11 REMS and Postmarketing Requirements and Commitments

11.1 Recommendations for Risk Evaluation and Mitigation Strategies

Prolia was initially approved with a REMS consisting of a Medication Guide (MG), communication plan (CP), and timetable for submission of assessments. The Prolia REMS goal was to mitigate the risks of hypocalcemia, osteonecrosis of the jaw (ONJ), atypical femur fracture (AFF), serious infections, and adverse dermatological reactions by informing healthcare providers (HCPs) and patients on these risks and to inform HCPs that they should counsel patients on these risks. On November 7, 2023, a Safety Labeling Change (SLC) was issued to update Prolia's labeling regarding the risk of severe hypocalcemia in patients with advanced chronic kidney disease. Following the SLC, a modification to the Prolia REMS was approved on March 5, 2024, to align the risk messaging in the REMS with the updated prescribing information (PI). The Prolia REMS goal was updated to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients. The REMS modification also removed the risks of ONJ, AFF, serious infections, and dermatologic reactions from the REMS and removed the MG as an element of the REMS.

On November 30, 2023, Celltrion submitted a BLA with a proposed REMS for Stoboclo that initially consisted of a MG, CP, and timetable for submission of assessments. The proposed REMS goal was to mitigate the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, serious infections, and dermatologic reactions, similar to the US Prolia REMS at the time of the BLA submission.

Due to the REMS modifications approved for the Prolia REMS on March 5, 2024, the Agency informed Celltrion on March 26, 2024, to update their REMS proposal for Stoboclo to align with the approved changes to the Prolia REMS. Celltrion submitted REMS amendments on April 24, 2024, and August 6, 2024, in response to the Agency's comments.

The Division of Risk Management (DRM) reviewed the amended REMS and found the Stoboclo REMS, submitted on August 6, 2024, acceptable. The Stoboclo REMS is comparable to the Prolia REMS and is designed to communicate the same key risk messages and achieve the same level of patient safety.

The Stoboclo REMS goal and objective are:

The goal of the Stoboclo REMS is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Stoboclo. The following describes the objective associated with the REMS:

Objective 1: Inform healthcare providers on:

- Risk of severe hypocalcemia in patients with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2)
- Need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Stoboclo in patients with advanced chronic kidney disease

The REMS elements consist of a Communication plan (CP) and timetable for submission of assessments.

The Communication Plan elements include:

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

Timetable for submission of assessments is at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS. The Stoboclo REMS assessment plan was reviewed by the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) and found to be acceptable.

11.2 Recommendations for Postmarket Requirements and Commitments

The following post-marketing requirement (PMR) and post-marketing commitment (PMC) will be requested:

PMR 4792-1: Provide an assessment of Stoboclo (denosumab-bmwo) for the treatment of glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age.

Final Report Submission: 06/2026

PMC 4792-2 To repeat the plunger movement study of the CT-P41 pre-filled syringe to ensure that sterility of the drug product is not impacted under worst case transportation conditions. This additional study will be performed using syringes with the worst-case plunger insertion depth (largest air bubble) considering the actual shipping condition of CT-P41.

Final Report Submission: 07/2025

PMC 4792-3 To conduct an additional endotoxin method verification with the [redacted] samples and assess the sample [redacted] This will ensure that the method is suitable for the detection of endotoxin per USP <85>. Three batches from the [redacted] samples will be used

Final Report Submission: 07/2025

Authors:

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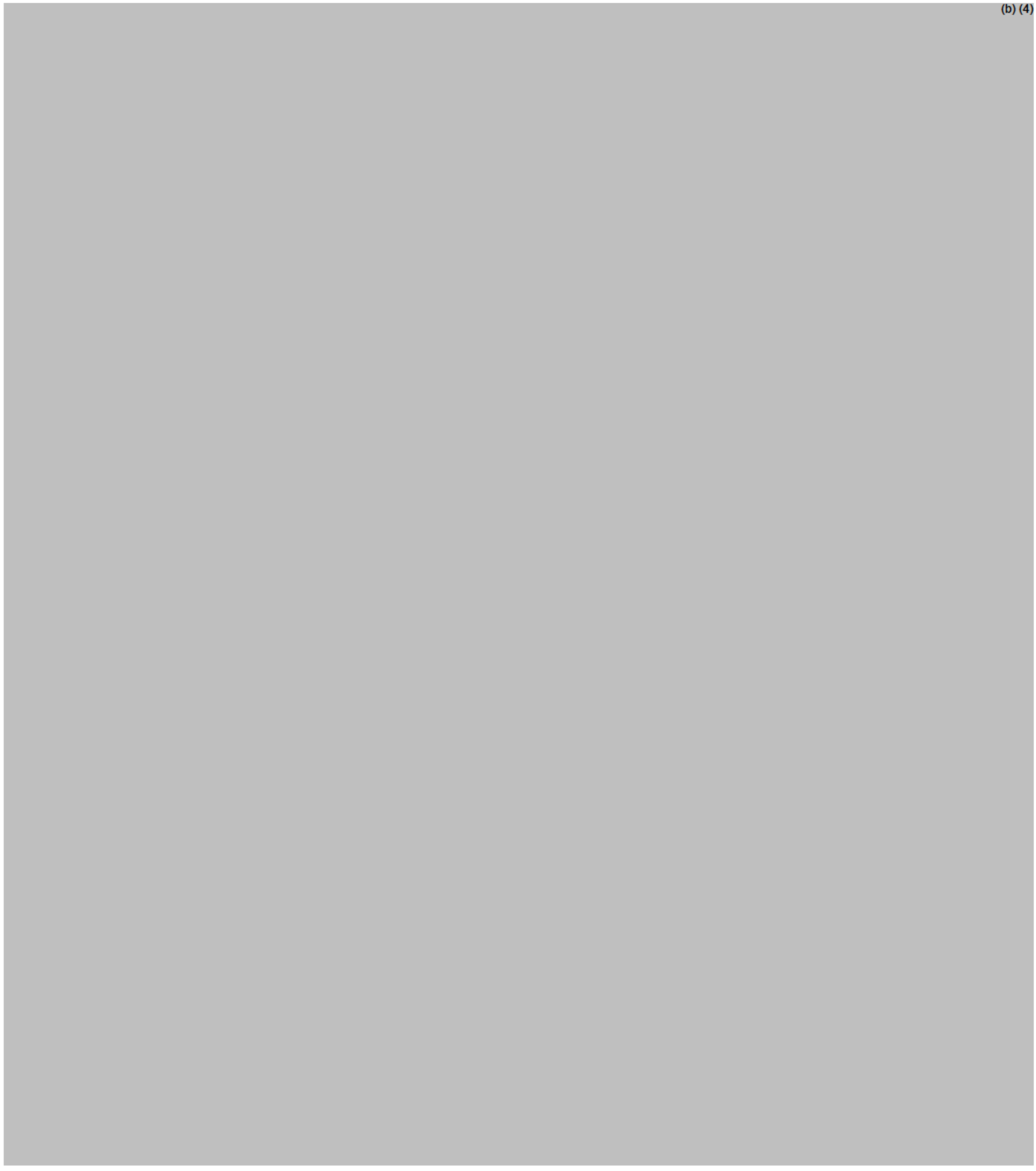
12 Division Director Comments

12.1 Division Director (OND – Clinical) Comments

I concur with the review team's assessment of the data and information submitted in this BLA. The data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrate that CT-P41 is biosimilar to US-Prolia and US-Xgeva. [redacted]

[redacted]



Author:
Theresa Kehoe, M.D
Division Director, Division of General Endocrinology

13 Appendices

13.1 Financial Disclosure

Covered Clinical Study: Study CT-P41 1.2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 6		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: Study CT-P41 3.1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 98		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.2 Clinical Pharmacology Appendices

Author: Clinical Pharmacology reviewers

13.2.1 Summary of Bioanalytical Method Validation and Performance

13.2.1.1 Pharmacokinetics

For the PK similarity study (1.2) and the efficacy and safety study (3.1), serum CT-P41, US-Prolia concentrations were measured using a validated Meso Scale Discovery-Electrochemiluminescent (MSD-ESL) (Method ICD 882). This method was suitable for assessment of PK of denosumab. The method validation entitled “Validation of an MSD-ECL Method for the Quantitation of CT-P41 (Denosumab) in Human Serum” and sample

analysis for the study were performed at [redacted](b) (4) In this method, Biotin-RANKL [redacted](b) (4) coated in 96-well plate was used to capture serum CT-P41, and U.S.- Prolia and Sulfo-Tag labeled HCA282 (Human Anti Denosumab) [redacted](b) (4) was used to detect the bound analytes. **Table 41** shows the summary of MSD-ESL method performance in quantification of CT-P41, and U.S.-Prolia during the method validation.

Table 41. Summary of bioanalytical method validation and in-study performance measurement of CT-P41 and US-Prolia

Bioanalytical method review summary	An MSD-Streptavidin (MSD-SA) coated plate is blocked and then coated with biotinylated-RANKL. CT-P41 present in samples are captured by biotinylated-RANKL. Sulfo-Tag labeled HCA282 is then used to detect CT-P41. In the presence of tripropylamine-containing read buffer, the Sulfo-Tag produces an ECL signal that is triggered when voltage is applied. Only samples that contain antibody bound to both biotinylated-RANKL and Sulfo-Tag labeled HCA282 will generate an ECL signal. The resulting electrochemiluminescence is measured in relative light units (RLU) using the Meso-Scale Discovery (MSD) SECTOR S 600 plate reader.	
Materials used for calibration curve & concentration	Human serum (pooled normal human serum)	
Validated assay range	10.0 (anchor), 20.0, 50.0, 100, 250, 500, 1000, 3000, 5000, and 6000 ng/mL	
Material used for QCs & concentration	Human serum (pooled normal human serum) QCs: 20.0, 50.0, 60.0, 450, 4500, 5000, and 6000 ng/mL	
Minimum required dilutions (MRDs)	1:20 in Blocker Casein in PBS	
Source & lot of reagents (LBA)	CT-P41 (Celltrion®) – 1P1A01, OP1A05 US Prolia - 1110020 Biotin-RANKL ([redacted](b) (4) – NB30710-182-01, NB23024-36-01 Sulfo Tag-HCA282 [redacted](b) (4)) – NB30710-189-01, NB23024-36-25, NB32888-182-29, NB30710-196-01, NB30710-168-01 HCA281 [redacted](b) (4) – 151087, 154017 RANKL [redacted](b) (4)) – B287633, B270743	
Regression model & weighting	Logistic Regression & 1/response²	
Validation Parameters	**Method Validation Summary**	**Acceptability**

<table>
<tr><td rowspan="3">Calibration curve performance during accuracy & precision
Per BMV,
At least 75% and minimum of 6 non-zero calibrators without anchor points and
LBA: ±20% bias (±25% at lower limit of quantitation (LLOQ)), ≤ 20%CV</td><td>No of standard calibrators from LLOQ to upper limit of quantitation (ULOQ): 10</td><td>Acceptable</td></tr>
<tr><td>Cumulative accuracy (%bias) from LLOQ to ULOQ
U.S.-Prolia: 90.75 – 105.18%
CT-P41: 94.35 – 102.7%</td><td>Acceptable</td></tr>
<tr><td>Cumulative precision (%CV) from LLOQ to ULOQ
U.S.-Prolia: 2.25 – 7.62%
CT-P41: 1.79 – 3.49%</td><td>Acceptable</td></tr>
<tr><td rowspan="3">QCs performance during accuracy & precision
Per BMV,
LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)</td><td>Cumulative accuracy (%bias) from LLOQ to ULOQ
U.S.-Prolia: 90.75 – 105.18%
CT-P41: 91.74 – 106.39%</td><td>Acceptable</td></tr>
<tr><td>Cumulative precision (%CV) from LLOQ to ULOQ
U.S.-Prolia: 2.25 – 7.62%
CT-P41: 3.03 – 15.2%</td><td>Acceptable</td></tr>
<tr><td>Percent total error (TE):
U.S.-Prolia: 5.20 – 15.2%
CT-P41: 5.32 – 21.6%</td><td></td></tr>
<tr><td>Drug Product Equivalence
(Acceptance criteria: 2 out of 3 replicates must meet acceptance
• %CV: ≤ 20.0% for QCs; ≤ 25.0% for LLOQ, back-up LLOQ, ULOQ, and back-up ULOQ
• % DFT: ± 20.0% for QCs; ± 25.0% for LLOQ, back-up LLOQ, ULOQ,</td><td>An evaluation of the equivalence between CT-P41 (denosumab) and US Prolia was performed by analyzing three replicate QCs, (20.0, 50.0, 60.0, 450, 4500, 5000, and 6000 ng/mL) of CT-P41 or US Prolia versus calibrators prepared from CT-P41.
<table>
<tr><td></td><td colspan="2">CT-P41</td><td colspan="2">US-Prolia</td></tr>
<tr><td>QC (ng/mL)</td><td>% CV</td><td>%DFT</td><td>% CV</td><td>%DFT</td></tr>
<tr><td>20</td><td>4.93</td><td>2.39</td><td>2.49</td><td>3.23</td></tr>
<tr><td>50</td><td>8.08</td><td>4.55</td><td>4.20</td><td>2.24</td></tr>
<tr><td>60</td><td>4.77</td><td>0.00</td><td>3.33</td><td>2.28</td></tr>
<tr><td>450</td><td>2.67</td><td>-7.03</td><td>2.94</td><td>-8.56</td></tr>
<tr><td>4500</td><td>4.49</td><td>-2.76</td><td>3.58</td><td>-2.54</td></tr>
<tr><td>5000</td><td>1.82</td><td>1.79</td><td>0.50</td><td>-5.15</td></tr>
<tr><td>6000</td><td>1.21</td><td>3.12</td><td>1.24</td><td>0.510</td></tr>
</table></td><td>Acceptable</td></tr>
</table>

<table>
<tr><td>and back-up ULOQ)</td><td></td><td></td></tr>
<tr><td>Selectivity & matrix effect (CT-P41 & US Prolia) (Acceptance criteria:
≥ 80% of blank samples must quantitate < LLOQ
• ≥ 80% of fortified samples must quantitate within ± 20.0% at high level and ± 25.0% at LLOQ)</td><td>10/10 unfortified individual healthy donors met the acceptance criteria.
9/10 individual healthy donors fortified at the LLOQ level, and 10/10 individual healthy donors fortified at the high QC level, met the acceptance criteria for CT-P41.
10/10 individual healthy donors fortified at the LLOQ level, and 10/10 individual healthy donors fortified at the high QC level, met the acceptance criteria for US Prolia.
9/10 unfortified individual disease state donors met the acceptance criteria.
9/10 individual disease state donors fortified at the LLOQ level, and 9/10 individual disease state donors fortified at the high QC level, met the acceptance criteria for CT-P41.
9/10 individual disease state donors fortified at the LLOQ level, and 9/10 individual disease state donors fortified at the high QC level, met the acceptance criteria for US Prolia.
[ICD 882 Version 1.02 Validation Report Addendum 1 Project Code RPLX3</td><td>Acceptable</td></tr>
<tr><td>Interference & specificity (CT-P41 & US Prolia)
ADA Intereference criteria:
• ≥ 80% blank sample results < their respective cut point(s).
• ≥ 80% of spiked matrix samples are expected be ≥ their respective cut point(s).
• Inhibited matrix lots:
○ 90% of spiked</td><td>ADA Interference (anti-CT-P41 NAb) (n = 10)
Matrix interference data in healthy and disease state individuals met the acceptance criteria (n=10).
<table>
<tr><td></td><td></td><td colspan="2">Healthy</td></tr>
<tr><td></td><td>CCP (%)</td><td>Average % Inhibition</td><td>SD</td></tr>
<tr><td>Unspiked Healthy</td><td rowspan="3">28.5</td><td>13.74</td><td>4.42</td></tr>
<tr><td>Spiked at 8 ng/mL Healthy*</td><td>41.3</td><td>4.90</td></tr>
<tr><td>Spiked at 1000 ng/mL Healthy</td><td>96.1</td><td>0.13</td></tr>
</table>
* needed confirmatory re-analysis to meet acceptable criteria; Data for acceptable criteria presented.
<table>
<tr><td></td><td></td><td colspan="2">Disease</td></tr>
<tr><td></td><td>CCP (%)</td><td>Average % Inhibition</td><td>SD</td></tr>
</table></td><td>Acceptable</td></tr>
</table>

<table>
<tr>
<td>sample results ≥ confirmatory cut point (CCP)
○ 90% of blank sample results < CCP

Target interference criteria:
• %CV between results at each control level must fall within the established precision of the method.
• Samples must produce mean results relative to their prepared concentrations: HPC > LPC ≥ cut point > blank</td>
<td>
<table>
<tr><td>Unspiked Diseased</td><td rowspan="3">31.4</td><td>1.52</td><td>7.46</td></tr>
<tr><td>Spiked at 8 ng/mL Diseased**</td><td>35.32</td><td>3.83</td></tr>
<tr><td>Spiked at 1000 ng/mL Diseased</td><td>95.74</td><td>0.11</td></tr>
</table>
** needed confirmatory re-analysis to meet acceptable criteria; Data for acceptable criteria presented; 1 subject did not meet acceptance criteria in confirmatory analysis

Target Interference (RANKL)
Negative control (NC), low positive control (PC), and high PC were each prepared with 0.00, 25.0, 50.0, and 100 pg/mL RANKL and analyzed. NC prepared with 50.0 pg/mL RANKL (AI 10) produced a positive result (< SCP) while NC prepared with 25.0 and 100 pg/mL of RANKL produced negative results (> SCP). To confirm the result, AI 10 was reanalyzed (n=2). Both replicates produced negative results. No target interference effect was observed up to 100 pg/mL RANKL.
[ICDIM 489 Validation Report (b) (4) Project Code RPLY2]
</td>
<td></td>
</tr>
<tr>
<td>Hemolysis effect (CT-P41 & US Prolia)
(Acceptance criteria:
• < LLOQ for blank hemolyzed samples
• %CV ≤ 20.0%
• %DFT ± 20.0% (± 25.0% at the LLOQ) for fortified</td>
<td>No effect from hemolysis up to 5% fully lysed whole blood on the quantitation of CT-P41 and US Prolia.
<table>
<tr><td></td><td colspan="3">CT-P41</td></tr>
<tr><td></td><td>Blank</td><td>LLOQ</td><td>HQC</td></tr>
<tr><td>% CV</td><td>0</td><td>5.32</td><td>3.15</td></tr>
<tr><td>% DFT</td><td><LLOQ</td><td>-13.4</td><td>-0.748</td></tr>
<tr><td colspan="4">US-Prolia</td></tr>
<tr><td></td><td>Blank</td><td>LLOQ</td><td>HQC</td></tr>
<tr><td>% CV</td><td>0</td><td>8.48</td><td>1.06</td></tr>
<tr><td>% DFT</td><td><LLOQ</td><td>-6.61</td><td>-0.435</td></tr>
</table>
</td>
<td>Acceptable</td>
</tr>
</table>

<table>
<tr><td>hemolyzed samples)</td><td></td><td></td></tr>
<tr><td>Lipemic effect (CT-P41 & US Prolia) (Acceptance criteria:
• < LLOQ for blank lipemic samples
• %CV ≤ 20.0%
• %DFT ± 20.0% (± 25.0% at the LLOQ) for fortified lipemic samples)</td><td>No effect from lipemia (> 300 mg/dL triglycerides) on the quantitation of CT-P41 and US Prolia.)
<table>
<tr><td colspan="4">CT-P41</td></tr>
<tr><td></td><td>Blank</td><td>LLOQ</td><td>HQC</td></tr>
<tr><td>% CV</td><td>0</td><td>0.701</td><td>2.56</td></tr>
<tr><td>% DFT</td><td><LLOQ</td><td>-12.5</td><td>-0.789</td></tr>
<tr><td colspan="4">US-Prolia</td></tr>
<tr><td></td><td>Blank</td><td>LLOQ</td><td>HQC</td></tr>
<tr><td>% CV</td><td>0</td><td>4.51</td><td>4.18</td></tr>
<tr><td>% DFT</td><td><LLOQ</td><td>-3.24</td><td>-2.17</td></tr>
</table></td><td>Acceptable</td></tr>
<tr><td>Dilution linearity (CT-P41 & US Prolia) (Acceptance criteria
• %CV ≤ 20.0%
• %DFT ± 20.0% for those samples within the calibration curve range)</td><td>Five replicate QCs containing 1,000,000 ng/mL CT-P41, and US Prolia, as 256-, 1024-, and 4096-fold dilutions were analyzed.
<table>
<tr><td colspan="4">CT-P41</td></tr>
<tr><td></td><td>Dilution 256</td><td>Dilution 1024</td><td>Dilution 4096</td></tr>
<tr><td>% CV</td><td>5.95</td><td>7.81</td><td>6.07</td></tr>
<tr><td>% DFT</td><td>8.62</td><td>1.85</td><td>4.31</td></tr>
<tr><td colspan="4">US-Prolia</td></tr>
<tr><td></td><td>Dilution 256</td><td>Dilution 1024</td><td>Dilution 4096</td></tr>
<tr><td>% CV</td><td>4.50</td><td>3.75</td><td>3.17</td></tr>
<tr><td>% DFT</td><td>6.55</td><td>-5.72</td><td>-8.41</td></tr>
</table></td><td>Acceptable</td></tr>
<tr><td>Hook effect (CT-P41 & US Prolia) (Acceptance criteria
• Results expected to be above the curve must be > ULOQ
• %CV ≤ 20.0%
• %DFT ± 20.0% for</td><td>A 1,000,000 ng/mL QC sample undiluted and serially diluted at 4-, 16-, 64-, 256-, 1024-, and 4096-fold dilutions. For the dilutions where the expected response or concentration after dilution should be above the highest calibration curve point, the measured concentrations were greater than the upper limit of quantitation. No apparent hook effect was observed at concentrations up to 1,000,000 ng/mL.</td><td>Acceptable</td></tr>
</table>

<table>
<tr><td>those samples within the calibration curve range)</td><td></td><td></td></tr>
<tr><td>Bench-top/process stability</td><td>Short-term stability at room temperature (RT): 25 hours</td><td>Acceptable</td></tr>
<tr><td>Freeze-Thaw stability (CT-P41 & US-Prolia) (Acceptance Criteria
• At least three values must be available to calculate stability statistics for each level tested
• %CV ≤ 20.0%
• %DFT ± 20.0%)</td><td>U.S.-Prolia: 6 cycles thawed at room temperature
CT-P41: 6 cycles thawed at room temperature
<table>
<tr><td></td><td colspan="2">CT-P41</td><td colspan="2">US-Prolia</td></tr>
<tr><td>Conc (ng/mL)</td><td>% CV</td><td>%DFT</td><td>% CV</td><td>%DFT</td></tr>
<tr><td>60</td><td>3.75</td><td>5.52</td><td>3.27</td><td>6.36</td></tr>
<tr><td>4500</td><td>2.74</td><td>4.95</td><td>2.34</td><td>3.83</td></tr>
</table></td><td>Acceptable</td></tr>
<tr><td>Long-term storage</td><td>U.S.-Prolia: 468 days at -80°C
CT-P41:468 days at -80°C</td><td></td></tr>
<tr><td>Parallelism</td><td>No interference caused by a matrix components
Overall precision of all dilutions for each sample was ≤ 30.0% for ten out of ten samples. All three dilutions for ten out of ten samples quantitated within the validated assay range</td><td>Acceptable</td></tr>
<tr><td>Carry over</td><td>Not applicable for ligand binding assays</td><td></td></tr>
<tr><td colspan="3">Method Performance in Study 1.2</td></tr>
<tr><td>Assay passing rate</td><td>127 runs performed; 126 runs were acceptable
Pass rate 99.2%</td><td>Acceptable</td></tr>
<tr><td>Standard curve performance</td><td>Cumulative bias range: -2.7 to 5.65%
Cumulative precision: 1.79 – 3.49% CV
Note: Data correspond to maximum and minimum accuracy and maximum %CV for the calibration curve of all accepted plates</td><td>Acceptable</td></tr>
<tr><td>QC performance</td><td>Cumulative bias range: -6.39 – 8.26%
Cumulative precision: 3.03 – 15.2% CV
• TE: 5.20 – 21.6%</td><td>Acceptable</td></tr>
</table>

	Note: Data correspond to maximum and minimum accuracy and maximum %CV for the calibration curve of all accepted plates	
Method reproducibility (Incurred Sample Reanalysis Acceptance criteria: • 10% of the samples should be reanalyzed • % difference should be within ± 30% for at least 2/3 of the repeats**)**	Overall % ISR Samples: 10% Total % ISR Samples to meet acceptance criteria: 99.7%	**Acceptable**
Study sample analysis/ stability	Samples were stored for a maximum of 286 days between sample collection and analysis. All samples were analyzed within the 468 days demonstrated long-term storage stability in human serum at -80° C (-90 °C to -60 °C).	
Method Performance in Study 3.1		
Assay passing rate	239 runs performed, 228 were acceptable; Pass rate 95.4%	**Acceptable**
Standard curve performance	Cumulative bias range: -2 to 1% Cumulative precision: ≤ 6% CV Note: Data correspond to maximum and minimum accuracy and maximum %CV for the calibration curve of all accepted plates	**Acceptable**
QC performance	Cumulative bias range: -6 to 3% Cumulative precision: ≤ 11% CV • TE: ≤ 16% Note: Data correspond to maximum and minimum accuracy and maximum %CV for the calibration curve of all accepted plates	**Acceptable**
Method reproducibility (Incurred Sample Reanalysis Acceptance criteria: • 10% of the samples should be reanalyzed	Overall % ISR Samples: 9.68% (ongoing) Total % ISR Samples to meet acceptance criteria: 99.6%	**Acceptable**

• % difference should be within ± 30% for at least 2/3 of the repeats**)**		
Study sample analysis/ stability	Samples were stored for a maximum of 449 days between sample collection and analysis. All samples were analyzed within the 468 days demonstrated long-term storage stability in human serum at -80° C (-90 °C to -60 °C).	

**Concentration data from impacted samples removed for PK analysis*
Sources: Bioanalytical Report for Study 1.2; Bioanalytical Report for Study 3.1; Other Analytical and Validation Report for Study 1.2; Other Analytical and Validation Report for Study 3.1; IR response from the Applicant to bioanalytical method comparability and QC bias comparison between CT-P41 and US-Prolia.

13.2.1.2 Pharmacodynamics

Serum carboxy terminal cross-linking telopeptide of type I collagen (s-CTX) and procollagen type 1 N-terminal propeptide (P1NP) in human serum were quantified using the electrochemiluminescence immunoassay (ECLIA) immunoassays from (b) (4) . The PD assays are based on commercially available in vitro diagnostic (IVD) kits, that were refined and fully validated with respect to precision, accuracy, parallelism, selectivity, dilution linearity, robustness, carry-over, and tested for stability (short-term, long-term, freeze/thaw cycles). Both the s-CTX and P1NP assays were additionally validated for the use of a 2-point calibration curve. Validations followed the requirements of the Clinical Lab Improvement Amendments (CLIA), College of American Pathologists (CAP), and Food and Drug Administration (FDA). All validation parameters passed the acceptance criteria, and the assays are considered appropriate for the quantification of s-CTX and P1NP in human serum.

13.2.2 Other Clinical Pharmacology Information

13.2.2.1 STUDY CT-P41 3.1

Title: A Double-blind, Randomized, Active-controlled, Phase 3 Study to Compare Efficacy, Pharmacokinetics, Pharmacodynamics, and Safety of CT-P41 and US-licensed Prolia in Postmenopausal Women with Osteoporosis

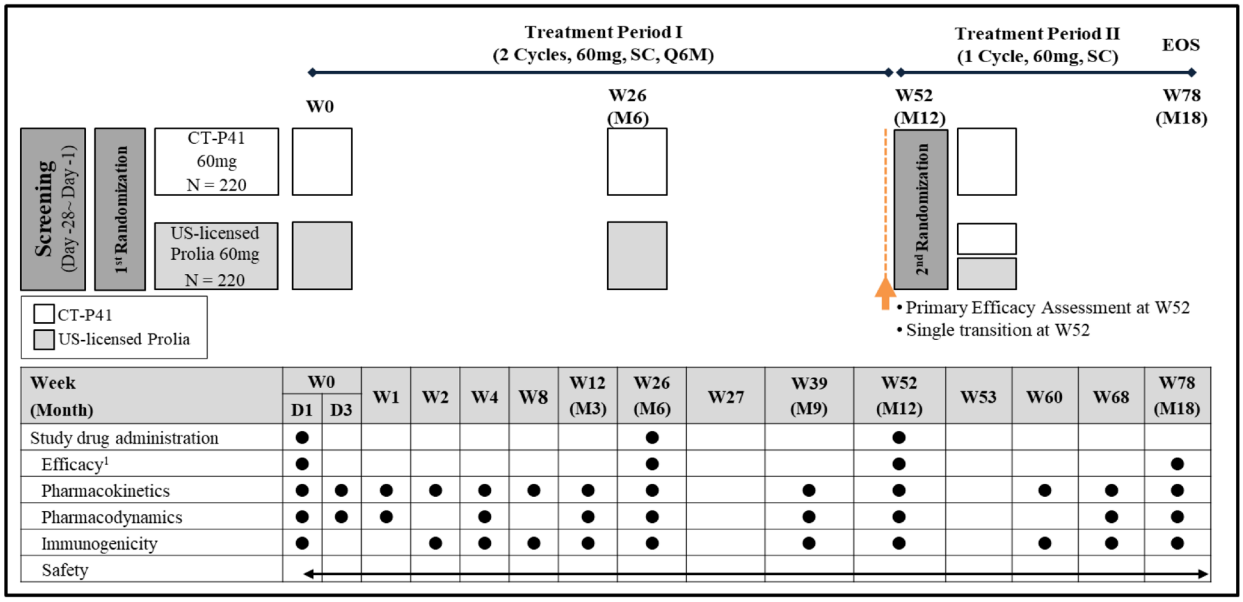
Objectives:

Primary Objective: 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

Secondary Objective: To evaluate the efficacy, pharmacokinetics (PK), pharmacodynamics (PD), and safety including immunogenicity of CT-P41 and US-licensed Prolia

Study Design: two-treatment period, randomized, double-blind, randomized, active-controlled, Phase 3 study (**Figure 12**). In Treatment Period I subjects were randomly assigned 1:1 to CT-P41 or US-Prolia group. At the end of 52 weeks, and beginning of Treatment Period II, subjects initially assigned to US-licensed Prolia in Treatment Period I were randomly assigned again in a ratio of 1:1 to either continue US-licensed Prolia (non-switching arm) or transition to CT-P41 (switching arm). Patients who were initially assigned to CT-P41 in Treatment Period I continued their treatment with CT-P41.

Figure 12: Study 3.1 Design Overview



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: BMD, bone mineral density; D, day; DXA, dual-energy X-ray absorptiometry; EOS, end-of-study; M, month; Q6M, every 6 months; SC, subcutaneous; US, United States; W, Week.
Source: Applicant Study Design Overview, Figure 9-1, Page 47; Study 3.1, Link to Study 3.1 CSR

Study Population: Postmenopausal female patients between the ages of 50 to 80 with BMD T-score at the lumbar spine (L1 to L4) ≤− 2.5 and ≥− 4.0. In treatment Period I subjects were stratified by age (< 65 years versus > 65 years), Baseline BMD at the lumbar spine (≤-3.0 versus > 3.0) and prior bisphosphonate therapy (yes versus no). In Treatment Period II subjects were stratified by change from baseline in BMD for lumbar spine at Week 52 (≥3% versus <3%). A total of 240 subjects (CT-P41 group) and 239 subjects (US-Prolia) enrolled and completed Treatment Period I. A total of 422 subjects were enrolled and included in the sample analysis with 221 patients, 100 patients, and 101 patients in the CT-P41 maintenance, US-Prolia maintenance, and switched to CT-P41 groups, respectively.

Drug Formulation and Administration:

- CT-P41, 60 mg by SC injection to the upper arm via PFS on Day 1 (Week 0), Week 26, and Week 52 (Treatment Period II)
- US-licensed Prolia, 60 mg by SC injection to the upper arm via PFS on Day 1 (Week 0), Week 26, and Week 52 (Treatment Period II)

- All subjects received daily supplementation of 1000 mg elemental calcium and at least 400 IU vitamin D.

PK Sampling (blood/serum) occurred at Week 0 (Day 1 and Day 3), Week 1 (Day 10), Week 2 (Day 15), Week 4 (Day 29), Week 8 (Day 57), Week 12 (Day 85), Week 26 (Day 183), Week 39 (Day 274), Week 52 (Day 365), Week 60 (Day 421), Week 68 (Day 477), and Week 78 (Day 547).

PD Sampling of bone turnover markers C-terminal telopeptide of type I collagen (s-CTX) and N-terminal propeptide of type I procollagen (P1NP) occurred Week 0 (Day 1 and Day 3), Week 1 (Day 10), Week 4 (Day 29), Week 12 (Day 85), Week 26 (Day 183), Week 39 (Day 274), Week 52 (Day 365), Week 68 (Day 477), and Week 78 (Day 547).

Immunogenicity Sampling (ADAs, NAb, and ADA titer; blood) occurred at Week 0 (Day 1), Week 2 (Day 15), Week 4 (Day 29) Week 8 (Day 57), Week 12 (Day 85), Week 26 (Day 183), Week 52 (Day 365), Week 60 (Day 421), Week 68 (Day 477), and Week 78 (Day 547). Pre-dose sampling was obtained on Days when treatment was administered (Day 1, Week 26, and Week 52).

PK Endpoints: The serum concentration and PK parameters (C_{max} and C_{trough}) were summarized by group using descriptive statistics including geometric mean and coefficient of variation (CV%).

PD Endpoints: Area under the effect curve (AUEC) of s-CTX, AUEC of P1NP, Percent change from baseline of s-CTX and P1NP at Weeks 26, 56, and 78.

PK Datasets Analyzed:

- Treatment Period I: The PK Set included 473 patients (237 and 236 patients in the CT-P41 and US-licensed Prolia groups, respectively) and 6 patients (3 patients each in the CT-P41 and US-Prolia groups, respectively) were excluded from the PK Set due to dosing issues on Day 1 or who did not have at least 1 post-treatment PK concentration data with a concentration above the LLoQ up to Week 52.
- Treatment Period II: The PK-Treatment Period II Subset included 388 patients (203 patients, 91 patients, and 94 patients in the CT-P41 maintenance, US-Prolia maintenance, and switched to CT-P41 groups, respectively). Of these, 34 patients (18 patients, 9 patients, and 7 patients in the CT-P41 maintenance, US-licensed Prolia maintenance, and switched to CT-P41 groups, respectively) who discontinued the study treatment due to the ongoing AE or who did not have at least 1 post-treatment PK concentration data with a concentration above the LLoQ after Week 52.

The Applicant's study design is predicated on multiple SC doses of CT-P41 or US-Prolia and follows the study subjects for ~1.5 years (547 days). The is appropriate as the US-Prolia is approved for dosing every 6 months SC. This also allowed the Applicant to

assess similarity between the US-Prolia arm and the CT-P41 arm when subjects were switched from US-Prolia to CT-P41.

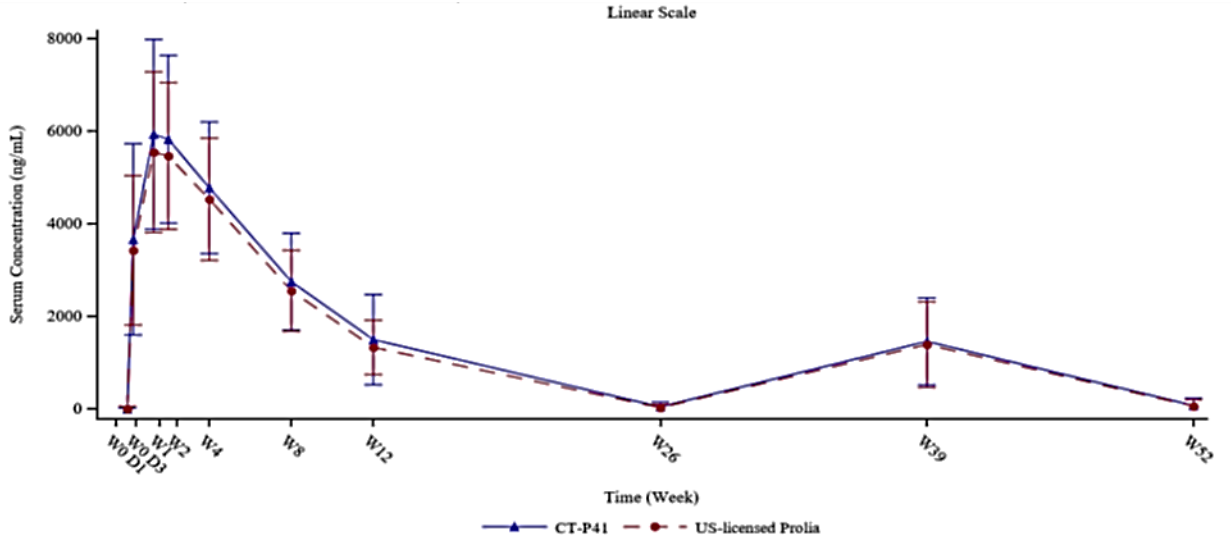
Bioanalytical PK Method and Performance

For the comparative clinical study (3.1) serum CT-P41, U.S.-Prolia concentrations were measured using a validated Meso Scale Discovery- Electrochemiluminescent (MSD-ECL). In this assay, an MSD-Streptavidin (MSD-SA) coated plate is blocked and then coated with biotinylated-RANKL. CT-P41 or US- Prolia present in samples are captured by biotinylated-RANKL. Sulfo-Tag labeled HCA282 is then used to detect CT-P41 or US-Prolia. In the presence of tripropylamine-containing read buffer, the Sulfo-Tag produces an ECL signal that is triggered when voltage is applied. Only samples that contain antibody bound to both biotinylated-RANKL and Sulfo-Tag labeled HCA282 will generate an ECL signal. The resulting electrochemiluminescence is measured in relative light units (RLU) using the Meso-Scale Discovery (MSD) SECTOR S 600 plate reader. Refer to the Appendix 14.1.1 for more detailed information on method validation.

PK Similarity Assessment

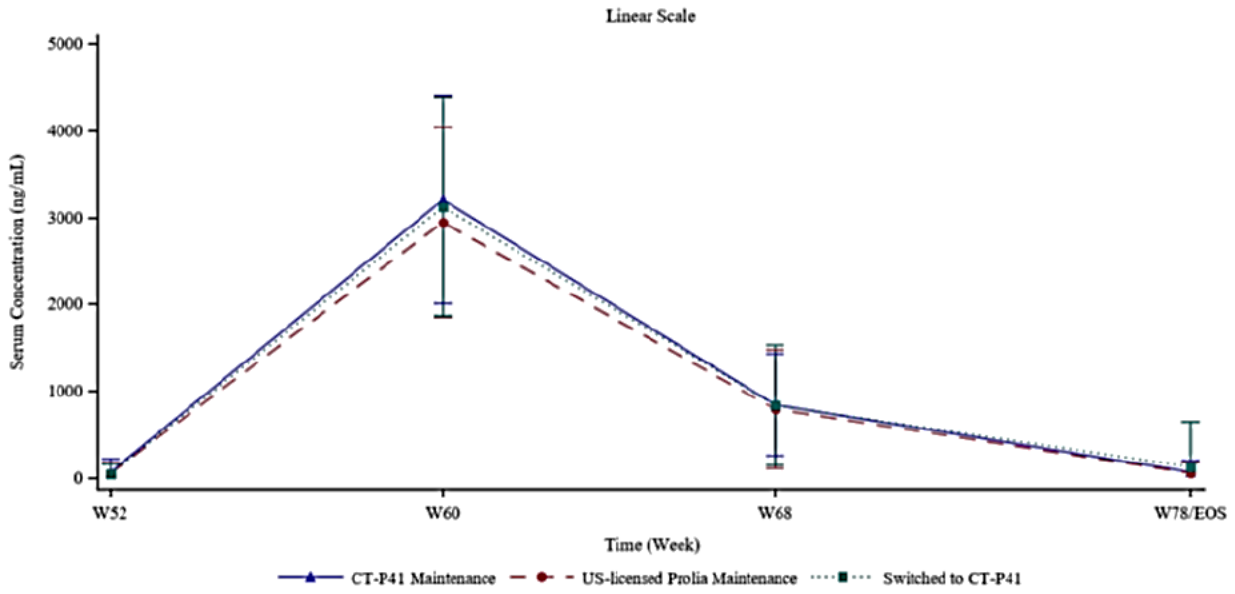
The mean CT-P41 and U.S.-Prolia concentration time -profiles are similar for Treatment Period 1(**Figure 13**) and Treatment Period 2 (**Figure 14**).

Figure 13: Mean (±SD) Serum Concentrations of Denosumab in Treatment Period I



Source: Figure 11-1, Page 178; Study 3.1, Link to Study 3.1 CSR

Figure 14: Mean (±SD) Serum Concentrations of Denosumab in Treatment Period II



Source: Figure 11-2, page 180, Study 3.1, Link to Study 3.1 CSR

Descriptive statistics for the C_{trough} (ng/mL) for the CT-P41 and US-Prolia groups in Treatment Period I and Treatment Period II demonstrate that denosumab concentrations between the groups was similar (**Table 42**). A similar trend was seen with C_{max} at Week 26 (Treatment Period I) (data not shown).

Table 42 - C_{trough} levels of denosumab in Treatment Periods I and II

Visit	CT-P41 C_{trough} (ng/mL)	US-Prolia C_{trough} (ng/mL)	Switched to CT-P41 C_{trough} (ng/mL)
Treatment Period I			
Week 0 (Day 1)			
n	227	221	
Mean (SD)	46.79 (105.102)	31.69 (73.253)	
Min, Max	0, 670.0	0, 388.0	
Week 26			
n	221	207	
Mean (SD)	75.64 (154.630)	63.99 (140.192)	
Min, Max	0, 1110.0	0, 972.0	
Treatment Period II			
Week 52			
n	199	90	93
Mean (SD)	73.52 (130.214)	61.55 (120.893)	129.93 (521.601)

Visit	CT-P41 C_{trough} (ng/mL)	US-Prolia C_{trough} (ng/mL)	Switched to CT-P41 C_{trough} (ng/mL)
Min, Max	0, 707.0	0, 490.0	0, 4900.0

Source: Table 11-20 (page 181), and Table 11-21 (page 181), Study 3.1,. Link to Study 3.1 CSR

Overall, the pharmacokinetics profiles in terms of denosumab concentrations were similar in all treatment groups throughout the study.

Bioanalytical PD Method and Performance

Bone turnover markers s-CTX and P1NP in human serum were quantified in human serum were quantified using the electrochemiluminescence immunoassay (ECLIA) immunoassays from (b) (4). The PD assays are based on commercially available in vitro diagnostic (IVD) kits, that were refined and fully validated with respect to precision, accuracy, parallelism, selectivity, dilution linearity, robustness, carry-over, and tested for stability (short-term, long-term, freeze/thaw cycles). Both the s-CTX and P1NP assays were additionally validated for the use of a 2-point calibration curve. Validations followed the requirements of the Clinical Lab Improvement Amendments (CLIA), College of American Pathologists (CAP), and Food and Drug Administration (FDA). All validation parameters passed the acceptance criteria, and the assays are considered appropriate for the quantification of s-CTX and P1NP in human serum.

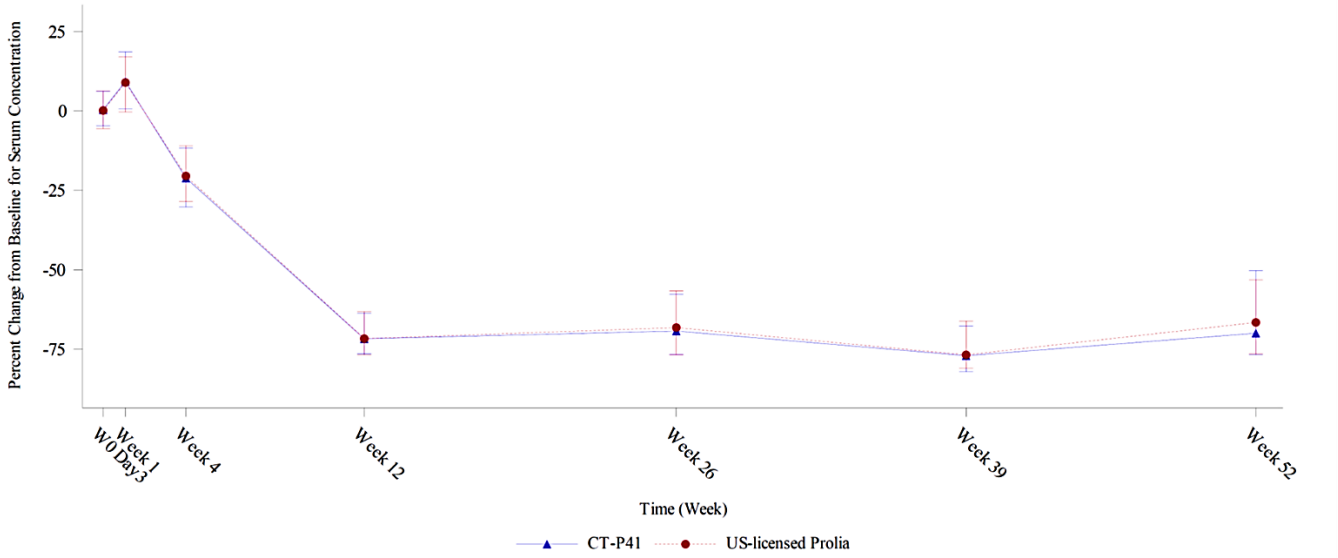
A summary of the bioanalytical validation report to assess the PD markers (s-CTX and P1NP) is included in the Clinical Pharmacology Appendices (Section 14.4.2). The analytical methods to determine s-CTX and P1NP concentrations are acceptable.

PD Similarity Assessment

The Applicant collected and analyzed PD data in the clinical studies, for which the results have been presented for completeness. These data were only evaluated to ensure the findings did not conflict with any of the results from the primary endpoint results from other assessments considered as part of decision-making as it pertains to the assessment of biosimilarity.

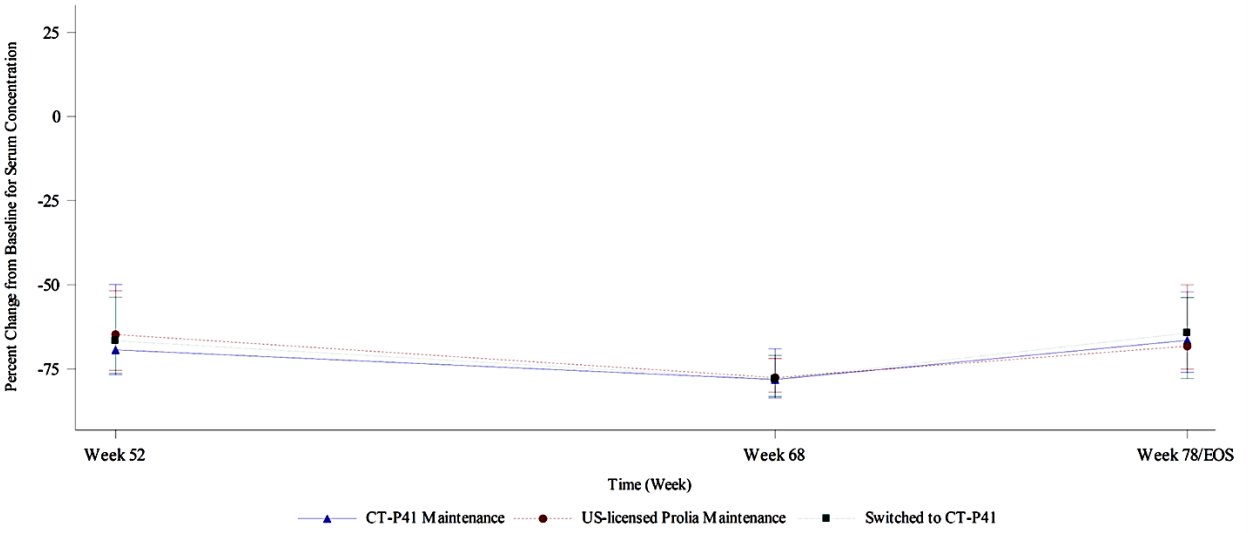
For the PD parameter in Study CT-P41 3.1 AUEC of %CfB in s-CTX (**Figure 15**) and P1NP (**Figure 16**) for Treatment Period I are reported. The PD profiles for both markers, s-CTX and P1NP, are similar for both treatment groups. A similar trend was observed for Treatment Period II (data not shown).

Figure 15 - Median Percent Change from Baseline for Serum Concentration of s-CTX versus Time in Treatment Period I



Source: Figure 11-3, page 185, Study 3.1, Link to Study 3.1 CSR

Figure 16 - Median Percent Change from Baseline for Serum Concentrations of P1NP versus Time in Treatment Period I



Source: Figure 11-6, page 187, Study 3.1, Link to Study 3.1 CSR

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

The Applicant collected and analyzed PD data in the clinical studies, for which the results have been presented for completeness. These data were only evaluated to

ensure the findings did not conflict with any of the results from the primary endpoint results from other assessments considered as part of decision-making as it pertains to the assessment of biosimilarity.

Actual value and percent change from baseline (%CfB) for serum concentration of s-CTX and P1NP for the CT-P41 and US-licensed Prolia treatment groups were collected and analyzed. The statistical analysis of log-transformed AUEC was conducted based on an ANCOVA model with treatment as a fixed effect and age and baseline value of s-CTX (or P1NP) as covariates to determine the ratio of geometric LS mean and 95% CIs for Study 1.2. For Study 3.1 the Applicant provided the Geometric Means (%CV) values for %CfB in CTX and P1NP without performing statistical analysis for similarity (GMR (%CV)).

Table 43: Geometric Mean AUEC of s-CTX and P1NP after treatment with CT-P41 or US-Prolia in Study 1.2

Treatment	Geometric Mean AUEC s-CTX (%CV)	Geometric Mean AUEC P1NP (day*%inhibition)
CT-P41	19294.9 (12.5)	12351.7 (24.2)
US-Prolia	18955.1 (11.8)	12822.2 (17.3)
GMR [95% CI]	101 [97.19, 105.68]	93.35 [83.55, 104.29]

Source: Data tabulated from Table 14.2.2.3, page 199, Study 1.2, Link to Study 1.2 CSR

Table 44: Geometric Mean AUEC %CfB of s-CTX and P1NP after treatment with CT-P41 or US-Prolia in Study 3.1

Treatment	Geometric Mean AUEC %CfB s-CTX (%CV) (day*%inhibition)	Geometric Mean AUEC %CfB P1NP (%CV) (day*%inhibition)
CT-P41	14059.26 (19.65)	7669.45 (28.34)
US-Prolia	14658.90 (14.51)	8856.24 (23.72)

Source: Data tabulated from Table 14.2.8.2, page 379, Study 3.1, Link to Study 3.1 CSR

13.3 Clinical Appendices

13.3.1 Schedule of Assessments, Study 3.1

Table 45. Schedule of Assessments, Study CT-P41 3.1

	Screen	Treatment Period I										Treatment Period II				EOS[1]
Week (Month)	−28 to −1	W0 (M0)		W1	W2	W4	W8	W12 (M3)	W26 (M6)	W27	W39 (M9)	W52 (M12)	W53	W60	W68	W78 (M18)
Day		1	3	10	15	29	57	85	183	190	274	365	372	421	477	547
Visit Window[2]		-			±1 day		±3 days				±5 days					
Informed consent	X															
Demographics	X															
Medical history	X															
Hepatitis B and C and HIV[3]	X								(X)			(X)				(X)
NYHA functional classification[4]	(X)															
Follicle-stimulating hormone	X															
Inclusion/Exclusion criteria	X	X5														
Randomization[6]		X										X				
Efficacy assessment – Predose, if study drug was administered on the same visit																
DXA scan[7]	X								X			X				X
Lateral spine X-rays (lumbar and thoracic)[8]	X								X			X				X
QoL assessment (OPAQ-SV, EQ-5D-5L)		X							X			X				X
Safety/Laboratory Test – Predose, if study drug was administered on the same visit																
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[10]	X								X			X				X
Height, BMI	X															
Weight	X	X		X		X		X	X		X	X			X	X
Physical examination[11]	X	X		X		X		X	X		X	X			X	X
Urinalysis[12]	X							X	X			X				X
Hematology, clinical chemistry[13]	X	X		X		X		X	X	X	X	X	X		X	X

Serum 25-OH vitamin D, albumin-adjusted total serum calcium (total Ca and serum albumin), phosphate, magnesium (local)[14]									X			X				
Immunogenicity/PK/PD Sampling – Predose, if study drug was administered on the same visit																
Immunogenicity sampling[15]		X			X	X	X	X	X		X	X		X	X	X
Pharmacokinetic sampling[16]		X	X	X	X	X	X	X	X		X	X		X	X	X
Pharmacydynamic sampling[17]		X	X	X		X		X	X		X	X			X	X
Study drug administration		X								X		X				
Hypersensitivity/allergic reaction monitoring[18] and injection site reaction[19]		X								X		X				
Local site pain by VAS[20]		X								X		X				
Vitamin D and Ca supplements treatment[21]		X														
radiography[22]		As required														
Prior/concomitant medications[23]	X	X														
AE monitoring[24]	X	X														

source: BLA 761404 SD1, module 5.3.5.1.0001 Study CT-P41 3.1, Table 9-2, p. 64-68

Abbreviations: AE, adverse event; BMD, bone mineral density; BMI; body mass index; Ca, calcium; DNA, deoxyribonucleic acid; DXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; eCRF, electronic case report form; EOS, end-of-study; EQ-5D-5L, EuroQoL-5 Dimensions-5 Levels Health Survey; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICF, informed consent form; IgM, immunoglobulin M; M, month: NYHA, New York Heart Association; OPAQ-SV, osteoporosis assessment questionnaire-short version; PD, pharmacodynamic; PK, pharmacokinetic; RNA, ribonucleic acid; QoL, quality of life; VAS, visual analog scale; W, week.

Note: For patients who discontinued study drug early or initiated different osteoporosis medication (including those prohibited by the protocol), every effort was to be made to complete scheduled study visits, and PK, PD, and immunogenicity samples were to be collected until the next study drug administration scheduled visit. If a patient discontinued study drug after administration of the study drug at Week 52, the PK, PD, and immunogenicity samples were to be collected until Week 78 visit. If a patient discontinued the study drug prior to Week 52, the patient was to return to the study center at Week 52 for the primary efficacy assessment. If a patient could not or was unwilling to attend any visit(s), a safety follow-up (e.g., AEs, concomitant medications) was to be conducted by telephone according to the study visit schedule.

1. An EOS visit was to occur at the Week 78 visit for all patients who completed or discontinued study drug.
2. A dosing visit window of ±3 days was allowed for Week 26 visit and that of ±5 days was allowed for Week 52 visit. If any study visit had to be rescheduled, subsequent visits were followed the original visit date scheduled.
3. At Screening, hepatitis B was assessed in all patients. A patient with past hepatitis B virus was allowed if resolved. If the patient developed hepatitis B reactivation, the study drug was to be stopped. Further eligibility for hepatitis B infection was confirmed according to the Table 9-3. At Screening, hepatitis C antibody was assessed in all patients. If hepatitis C antibody test result was positive, a HCV RNA test was performed at Screening. If the HCV RNA test result was positive, the

patient was excluded from the study; If the HCV RNA test result was negative, the patient could be included in the study at the investigator's discretion. Further evaluation for the patients who were enrolled based on HCV RNA test could be done depending on the investigator's discretion during the study. HIV test was assessed in all patients at Screening. If the HIV test result was positive, the patient was excluded from the study. Hepatitis B, hepatitis C, and HIV analysis were performed at the central laboratory.

4. At Screening, patients who had history of heart failure were assessed for the presence of congestive heart failure according to the NYHA functional classification.
5. The inclusion and exclusion criteria were confirmed by screening results prior to the randomization on Day 1.
6. Patients were randomly assigned to one of two groups (either CT-P41 or US-licensed Prolia) on Day 1 prior to the study drug administration. Second randomization was performed prior to the study drug administration on Week 52. Patients who were initially randomized to CT-P41 in Treatment Period I continued to receive CT-P41. Patients who were initially randomized to US-licensed Prolia in Treatment Period I, were randomly assigned again in a ratio of 1:1 to switching arm (CT-P41) or non-switching arm (US-licensed Prolia).
7. 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 was to be performed at a central imaging vendor. If needed, Week 26 DXA scan could be occurred at a separate site visit within ±3 days visit window of Week 26 visit, which was followed by the study drug administration occurring within the same visit window of Week 26 visit. At Week 52 visit, the DXA scan was analyzed by both the central imaging vendor and the study center. If needed, Week 52 DXA scan could be occurred at a separate site visit within ±5 days visit window of Week 52 visit, which was followed by the study drug administration occurring within the same visit window of Week 52 visit. A BMD assessor for the local reading was assigned to each study center. If possible, it was recommended that the local reading was to be performed by the same person at each study center throughout the study period. The local reading result at Week 52 was used for the stratification factor of the second randomization.
8. Lateral spine X-ray was 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. If needed, the lateral spine X-ray at Week 26 or Week 52 could occur at a separate site visit within ±3 days or ±5 days visit window of Week 26 or Week 52 visit respectively, which was followed by the study drug administration occurring within the same visit window of Week 26 or Week 52 visit.
9. Vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) were measured after 5 minutes of rest (sitting).
10. All scheduled 12-lead ECG were performed at the study center after the patients had rested in a supine position for at least 5 minutes prior to recording of 12-lead ECG. Regardless of the 12-lead ECG result, further cardiological evaluation could be conducted at the investigator's discretion.
11. Physical examination including oral examination (including mouth, gums, teeth, tongue).
12. Urinalysis analysis was performed at the central laboratory.

Urinalysis	Color, pH, specific gravity, ketones, protein, glucose, bilirubin, leukocytes, nitrite, urobilinogen, occult blood, and microscopic examination (only if urinalysis dipstick results were abnormal).

13. Hematology, clinical chemistry, and other test samples were analyzed at the central laboratory. Clinical monitoring of albumin-adjusted total serum calcium, serum 25-OH vitamin D, and mineral levels magnesium, phosphate), and any sign and symptoms of hypocalcaemia were to be closely conducted and adequately treated at the investigator's discretion, if occurred.

Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential count, absolute neutrophil count, lymphocyte count, and platelets count
Clinical chemistry	Albumin, albumin-adjusted total serum calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, chloride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatine kinase-myocardial band isoenzyme, creatine phosphokinase, creatinine, gamma-glutamyl transferase, glucose, lactate dehydrogenase, triglycerides, magnesium, phosphate, potassium, sodium, total bilirubin, direct bilirubin, total protein, uric acid, Troponin I, serum 25-OH vitamin D, thyroid stimulating hormone, and intact parathyroid hormone

14. Clinical laboratory results including serum 25-OH vitamin D, albumin-adjusted total serum calcium, phosphate, and magnesium were obtained to determine the study drug administration at Weeks 26 and 52. The clinical laboratory tests were monitored for hypocalcaemia and were analyzed at the local laboratory. If abnormal results were reported, patients were treated accordingly, and follow-up actions was to be taken at the investigator's discretion. If needed, the tests could be occurred at a separate site visit within ± 3 days visit window of Week 26 visit or within ± 5 days visit window of Week 52 visit, which was followed by the study drug administration occurring within the same visit window of each visit. Albumin-adjusted total serum calcium level was calculated using: Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 − serum albumin [g/dL]), where 4.0 represents the average albumin level. If the albumin-adjusted total serum calcium level was calculated using mg/dL unit, it could be adjusted for SI units as: Corrected calcium (mmol/l) = total Ca (mmol/l) + 0.02 (40 – serum albumin [g/l]).
15. Samples for immunogenicity testing were collected prior to dosing of the study drug if study drug was administered on the same visit. Other samples could be taken at any time of the scheduled visit. Additional immunogenicity was to be assessed when immune-related AEs occurred. Analysis was performed at the central laboratory. For patients who early discontinued study drug, immunogenicity samples were collected until the next study drug administration scheduled visit and further immunogenicity sampling was unnecessary. When a patient discontinued study drug after administration of the study drug at Week 52, the immunogenicity samples were to be collected until Week 78 visit.
16. Samples for PK testing were collected up to 30 minutes prior to dosing of the study drug if study drug was administered on the same visit. Other samples could be taken at any time of the scheduled visit. Analysis was performed at the central laboratory. For patients who early discontinued study drug, PK samples were collected until the next study drug administration scheduled visit and further PK sampling was unnecessary. When a patient discontinued study drug after administration of the study drug at Week 52, PK samples were to be collected until Week 78 visit.
17. Samples for PD testing were taken in the morning after fasting overnight for 8 hours prior to assessment, and the patients had to refrain from intense exercise the day prior to PD assessment. Analysis was performed at the central laboratory. For patients who early discontinued study drug, PD samples were collected until the next study drug administration scheduled visit and further PD sampling was unnecessary. When a patient discontinued study drug after administration of the study drug at Week 52, PD samples were to be collected until Week 78 visit.
18. Vital signs including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (before the start of the study drug administration [within 15 minutes] and at 1 hour [± 10 minutes] after the end of the study drug administration) were assessed to monitor for possible hypersensitivity reactions. In addition, hypersensitivity was monitored by routine continuous clinical monitoring including patient-reported signs and symptoms. In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen and artificial ventilation were available and any types of ECG could be performed. For patients who early discontinued study drug, monitoring of hypersensitivity/allergic reactions was unnecessary after the discontinuation.
19. Injection site reaction was assessed 30 minutes (±10 minutes) after the end of administration of the study drug. For patients who early discontinued study drug, assessment of injection site reaction was unnecessary after the discontinuation.
20. Patients assessed local site pain using 100 mm VAS immediately (not exceeding 15 minutes) after the end of administration of the study drug. For patients who early discontinued study drug, assessment of local site pain was unnecessary after the discontinuation.
21. All patients were also to be received daily supplementation containing at least 1,000 mg of elemental calcium and at least 400 IU vitamin D from randomization to EOS visit. The information about calcium and vitamin D administration was to be collected via patient's diary and was also to be recorded in both the source documents and eCRF.
22. Radiography was performed as required for confirmation of suspected fractures. Radiography was analyzed at a central imaging vendor.
23. Use of all prior and concomitant medication from the 30 days prior to the signed date of ICF until the EOS was to be recorded. Use of all prior and concomitant medications for the treatment of osteoporosis, from the diagnosis of disease until the EOS visit, was to be recorded. For eligibility check, relevant medication history was also recorded.
24. Adverse events were to be assessed from the signed date of ICF until EOS visit, regardless of the relationship to the study drug. The condition of the patient was to be monitored throughout the study for any signs or symptoms. After the last EOS visit, serious adverse drug reactions were to be reported to CELLTRION, Inc. or its designee.

Entry Criteria, Study 3.1

Inclusion Criteria

1 Women aged 50 to 80 years, both inclusive.

2 Body weight between 40.0 and 99.9 kg, both inclusive, when rounded to the nearest tenth.

2 Postmenopausal, as defined by:

a) No menstrual period for at least 12 consecutive months prior to the Screening visit with FSH level ≥30 mIU/mL assessed by central laboratory at Screening visit, or
b) Surgical menopause (bilateral oophorectomy with or without hysterectomy) ≥12 months prior to the Screening visit

3 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.

4 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.

5 Patient with albumin-adjusted total serum calcium ≥8.5 mg/dL (≥2.125 mmol/L) at Screening.

6 Patient had adequate hepatic function at Screening as defined by the following clinical chemistry results:

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN)
- Alkaline phosphatase (ALP) ≤2 × ULN and total bilirubin ≤2 × ULN

7 In good general health as determined by medical history, physical examination, and laboratory tests and able to walk without assistance, at the investigator's discretion.

8 Patient and/or their legally authorized 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.

9 Patient with a hypersensitivity to any component of denosumab or dry natural rubber (a derivative of latex).
10 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.
11 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 hospitalization, 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

12 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 [Genant *et al*., 1993]) 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)
e) Current hypothyroidism (unless well controlled on stable thyroid replacement therapy)
f) Bone disease and metabolic disease (except for osteoporosis) that might interfere with the interpretation of the results including osteomalacia, osteogenesis imperfecta, Paget's disease, rheumatoid arthritis, ankylosing spondylitis, osteopetrosis, fibrous dysplasia, an elevation of ALP at the investigator's discretion, Cushing's disease, hyperprolactinemia, malabsorption syndrome, advanced scoliosis or extensive lumbar fusion
g) History of severe skeletal pain with bisphosphonates
h) 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

i) 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
j) 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

13 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) Hemoglobin <10 g/dL

14 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 (estrogen with or without progestogen), selective estrogen-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, anticonvulsives (except benzodiazepines), systemic ketoconazole, anabolic steroids, testosterone, androgens, adrenocorticotropic hormone, cinacalcet, aluminum, 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 authorized 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.

Secondary Endpoints in Study CT-P41 3.1

There were no key efficacy confirmatory secondary endpoints prespecified in this study. There were no multiplicity adjustments made for the secondary endpoints. These endpoints are used as exploratory endpoints to support the primary endpoint. Tables 3-5 show the summary statistics for the secondary endpoints.

Table 46 shows the descriptive statistics for BMD for lumbar spine (L1 to L4) at week 26.

Table 46: BMD for Lumbar Spine (L1 to L4) Summary Statistics by Treatment Group and Visit, Treatment Period 1 Full Analysis Set, Study CT-P41 3.1

Timepoint	CT-P41 N=239	US-Prolia N=238
Baseline		
n	239	238
Mean (SD)	0.75 (0.07)	0.74 (0.06)
Min-Max	0.61-0.88	0.61-0.88
Week 26		
n	225	219
Mean (SD)	0.77 (0.07)	0.77 (0.07)
Min-Max	0.62-0.94	0.61-0.96
% Change from baseline 26		
n	225	219
Mean (SD)	3.79 (3.42)	3.48 (3.47)
Min-Max	-4.94-12.78	-5.42-14.09

Source: Statistical Reviewer's Analysis; adsl.xpt, addxa.xpt
Abbreviations: BMD for lumbar spine; N, total number of subjects; n, total number of subjects at that timepoint; SD, standard deviation

Table 47 shows the descriptive statistics for TH-BMD.

Table 47: TH-BMD (g/cm2) Summary Statistics by Treatment Group and Visit, Treatment Period 1 Full Analysis Set, Study CT-P41 3.1

Timepoint	CT-P41 N=239	US-Prolia N=238
Baseline		
n	239	238
Mean (SD)	0.76 (0.09)	0.76 (0.09)
Min-Max	0.50-1.02	0.52-1.05
Week 26		
n	222	218
Mean (SD)	0.77 (0.09)	0.77 (0.09)
Min-Max	0.50-1.04	0.50-1.02
% Change from baseline 26		
n	222	218
Mean (SD)	1.79 (2.55)	1.29 (2.78)
Min-Max	-7.34-11.04	-6.57-12.12
Week 52		
n	219	212
Mean (SD)	0.78 (0.09)	0.77 (0.09)
Min-Max	0.50-1.04	0.52-1.01
% Change from baseline 52		
n	219	212
Mean (SD)	2.79 (2.87)	2.43 (2.84)
Min-Max	-6.11-12.35	-8.62-12.40

Source: Statistical Reviewer's Analysis; adsl.xpt, addxa.xpt
Abbreviations: TH-BMD, total hip bone mineral density; N, total number of subjects; n, total number of subjects at that timepoint; SD, standard deviation

Table 48 shows the descriptive statistics for Total Femoral Neck.

Table 48: Femoral Neck Summary Statistics by Treatment Group and Visit, Treatment Period 1 Full Analysis Set, Study CT-P41 3.1

Timepoint	CT-P41 N=239	US-Prolia N=238
Baseline		
n	239	238
Mean (SD)	0.67 (0.10)	0.67 (0.11)
Min-Max	0.38-0.96	0.46-0.99

Timepoint	CT-P41 N=239	US-Prolia N=238
Week 26		
n	222	218
Mean (SD)	0.68 (0.11)	0.68 (0.11)
Min-Max	0.42-0.98	0.45-1.02
% Change from baseline 26		
n	222	218
Mean (SD)	1.57 (3.58)	1.23 (3.67)
Min-Max	-14.35-13.71	-11.06-11.77
Week 52		
n	219	212
Mean (SD)	0.69 (0.10)	0.68 (0.11)
Min-Max	0.43-0.99	0.47-1.02
% Change from baseline 52		
n	219	212
Mean (SD)	2.23 (4.02)	1.95 (3.87)
Min-Max	-10.20-14.92	-9.20-16.17

Source: Statistical Reviewer's Analysis; adsl.xpt, addxa.xpt
Abbreviations: N, total number of subjects; n, total number of subjects at that timepoint; SD, standard deviation

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/s/

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