CELLTRION Inc.
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

Statistical Analysis Plan
Version 1.1 (A)
January 10, 2024

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Upon review of this document, including table, listing and figure shells, the undersigned approves the final statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing and figure production can begin.

Approved by: _____ Date: ____/____/____

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AUEC	Area under the Effect Curve
BMD	Bone Mineral Density
CI	Confidence Interval
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DRM	Data Review Meeting
DXA	Dual-energy X-ray Absorptiometry
ECGs	Electrocardiograms
eCRF	Electronic Case Report Form
EOS	End-of-Study
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels Health Survey
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
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
HCV RNA	Hepatitis C virus RiboNucleic Acid
HBV DNA	Hepatitis B virus Deoxyribonucleic Acid
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
ICF	Informed Consent Form
ITT	Intent-to-Treat
ISR	Injection Site Reaction
IU	International Unit
IWRS	Interactive Web Response System
LLoQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MAR	Missing at Random
MI	Multiple Imputation

MNAR	Missing Not at Random
NAb	Neutralizing Antibody
NYHA	New York Heart Association
OPAQ-SV	Osteoporosis Assessment Questionnaire Short Version
P1NP	Procollagen type 1 N-terminal Propeptide
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPS	Per-Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s-CTX	Serum Carboxy-terminal Cross-linking Telopeptide of Type I Collagen
SD	Standard Deviation
SI	System International
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
ULoQ	Upper Limit of Quantification
VAS	Visual Analog Assessment
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) defines the statistical methods and data presentations to be used by CELLTRION, Inc. (hereinafter referred to as "CELLTRION") Clinical Statistics team in the analysis and presentation of data from CELLTRION study number CT-P41 3.1, entitled as "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".

There are two clinical study reports (CSRs) planned for the following time points:

- 1st CSR: After all eligible patients have completed the Week 52 assessment
- Final CSR: After all patients have completed or terminated from the study

This SAP is based on the following documents:

- Study Protocol Version 2.1, including country specific A.0 – 18 April 2022
- Unique Case Report Form Version 3.0 – 09 May 2022

1.1. Data Cut-off for Analysis

The data cut of the 1st CSR proceeds as follows:

- Patients who signed the informed consent form between May and August, 2021: all data will be included.
- Patients who signed informed consent form in April, 2022: The visit-based data collected up to Week 52 will be included. The non visit-based data collected at or prior to the last assessment date of Week 52 will be included.

  For patients who have terminated the study participation early (on or before Week 52), all data collected will be included.

The final CSR will include all data collected up to the completion or early termination of all patients from the study.

2. STUDY OBJECTIVE

Primary and secondary objectives are described as below.

2.1. 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

2.2. Secondary Objective

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

3. OVERALL STUDY DESIGN AND PLAN

This is a double-blind, randomized, active-controlled, Phase 3 study to evaluate the efficacy, PK, PD, and safety including immunogenicity of CT-P41 compared with US-licensed Prolia in postmenopausal women with osteoporosis.

Approximately 440 patients with postmenopausal osteoporosis will be enrolled and randomly assigned to receive 60 mg of CT-P41 or US-licensed Prolia. All patients will also receive daily supplementation containing at least 1,000 mg of elemental calcium and at least 400 international unit (IU) vitamin D from randomization to end-of-study (EOS) visit and the data will be collected via patient's diary.

The study will comprise of 4 study periods (Screening Period, Treatment Period I, Treatment Period II, and EOS visit) and the duration of the study will be up to 82 weeks.

- Screening Period (from Day -28 to Day -1)
- Treatment Period I (from Week 0 to Week 52 predose)
- Treatment Period II (from Week 52 to prior to Week 78 [EOS visit])
- EOS visit (Week 78)

3.1. Screening Period

Screening evaluations will be completed within 28 days prior to the randomization.

3.2. Treatment Period I

On Day 1, Week 0, patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study and randomly assigned in a 1:1 ratio to 1 of 2 treatment groups to receive 60 mg of CT-P41 or US-licensed Prolia. Patients will receive a total of 2

doses of 60 mg of CT-P41 or US-licensed Prolia at Day 1, Week 0 (the same date of the randomization) and Week 26.

The primary efficacy endpoint of percent change from baseline in BMD for lumbar spine (L1 to L4) will be measured at Week 52. Efficacy, PK, PD, and safety including immunogenicity data will be also collected.

3.3. Treatment Period II

All patients who completed Treatment Period I will undergo the second randomization process prior to the study drug administration at Week 52 and will enter the Treatment Period II to receive an additional 1 dose of study drug.

Patients who are initially randomized to CT-P41 in Treatment Period I will continue to receive CT-P41. Patients who are initially randomized to US-licensed Prolia in Treatment Period I, will be re-randomized in a 1:1 ratio to switching arm (CT-P41) or non-switching arm (US-licensed Prolia). The study drug during the Treatment Period II will be given at Week 52 study visit. All assessments including efficacy, PK, PD, and safety including immunogenicity will be performed.

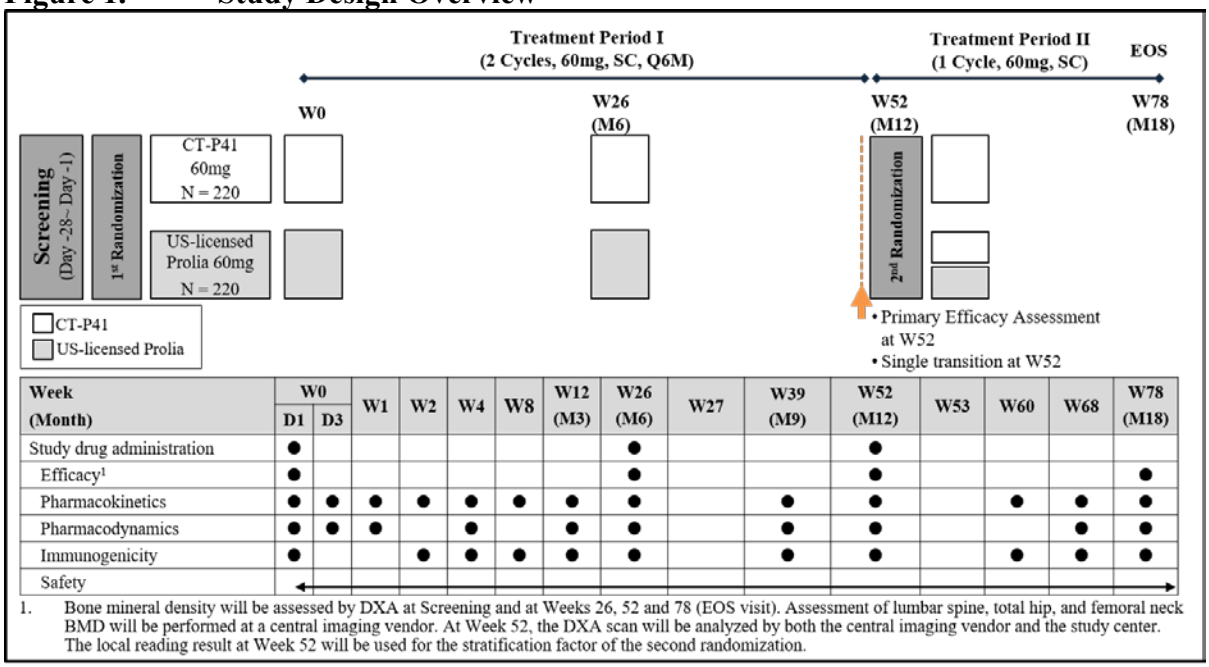
3.4. End-of-Study Visit

The EOS visit will be performed at Week 78 and assessments including efficacy, PK, PD, and safety including immunogenicity will be performed.

For patients who discontinue the study treatment early or initiate different osteoporosis medication (including those prohibited by the protocol), every effort should be made to complete regularly scheduled study visits for planned clinical assessments, and PK, PD, and immunogenicity samples will be collected until the next study drug administration scheduled visit. When a patient discontinues the study treatment at Week 52, the PK, PD, and immunogenicity samples will be collected until Week 78 visit. Especially, if a patient discontinues the study treatment prior to Week 52, the patient should return to the study center at Week 52 for the primary efficacy assessment. If a patient cannot or is unwilling to attend any visit(s), a safety follow-up (e.g., adverse events [AEs], concomitant medication) will be conducted by telephone according to the study visit schedule.

The study design and patient assessment overview are presented in Figure 1.

Figure 1. Study 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	←														→

1. Bone mineral density will 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 will be performed at a central imaging vendor. At Week 52, the DXA scan will be analyzed by both the central imaging vendor and the study center. The local reading result at Week 52 will be used for the stratification factor of the second randomization.

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.

4. GENERAL STATISTICAL CONSIDERATIONS

Continuous data will be summarized using descriptive statistics: number of patients (n), mean, standard deviation (SD), minimum, median and maximum, unless otherwise specified. The descriptive statistics will be calculated using original data before rounding although rounded values are listed. The following rules will be applied with regards to the number of decimal places:

- Minimum and maximum will be presented to the same number of decimal places as reported.
- Mean, Q1 (the first quartile), median, Q3 (the third quartile), geometric mean and coefficient of variation (CV, %) will be rounded to one more decimal place than the maximum decimal place of values in the source listing.
- SD will be rounded to one more decimal place than mean.

For the original data with 3 or more decimal places (recorded data in eCRF and calculated data; e.g. percent change from baseline in BMD), the reported/maximum decimal places in the rules above will be regarded as 3 when determining the number of decimal places presented in descriptive statistics summaries and the values rounded to 3 decimal places will be presented in listings.

Geometric mean will not be reported if the dataset includes zero or negative values and CV (%) will not be reported if the mean is zero.

Results collected with inequality sign are set to the respective limit (e.g. use 4 for '>4' and use 100 for '<100') unless otherwise specified.

Categorical data will be summarized using frequency tables showing numbers and percentages of patients. Percentages will be presented to one decimal place and will be suppressed when the count is zero. A row denoted 'Missing' will be included in count tabulations where necessary to account for missing values. The denominator for all percentages will be the number of patients within each treatment group for the analysis sets of interest, unless otherwise specified.

Unscheduled visit will not be summarized in visit-based tables, unless otherwise specified. However, all data will be displayed in listings. Listings will be sorted by the treatment group, patient number and visit, if applicable. In cases where additional sorting is required, other variables will be included in sorting as applicable.

4.1. Software

[redacted]

4.2. Sample Size

A sample size of 440 patients (220 patients in each treatment group of CT-P41 and US-licensed Prolia) will achieve approximately 90% statistical power for the demonstration of similarity of percent change from baseline in BMD for lumbar spine at Week 52, based on the two one-sided 5% significance level and an equivalence margin of ± 1.45%. In this sample size calculation, the common SD is assumed to be 4.0% and the expected mean difference of percent change from baseline to be 0. The dropout rate has been hypothesized as 20%.

4.3. Randomization, Stratification, and Blinding

An interactive web response system (IWRS) will be used for the randomization. Unblinded biostatisticians in contract research organization will generate the randomization schedule for IWRS, which will link patient randomization IDs to treatment codes. The randomization will be balanced by using permuted blocks.

Approximately 440 patients will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups (approximately each 220 patients in the CT-P41 and US-licensed Prolia) on Day 1 (Week 0) prior to the study drug administration.

The first randomization will be stratified by:

- Age (<65 *versus* ≥65)
- Baseline BMD T-score at the lumbar spine (≤-3.0 *versus* >-3.0)
- Prior bisphosphonates therapy (Yes *versus* No)

The second randomization will be performed at Week 52 prior to the study drug administration. Patients in the US-licensed Prolia treatment group will be randomly assigned again in a ratio of 1:1 to either switching treatment group (CT-P41) or non-switching treatment group (US-licensed Prolia). All patients who were initially randomly assigned to the CT-P41 at the first randomization will continue their treatment. The second randomization process will be conducted in all patients to maintain the study blind.

The second randomization for US-licensed Prolia treatment group will be stratified by:

- Change from baseline in BMD for lumbar spine at Week 52 (≥3% versus <3%) (baseline: central reading; Week 52: local reading)

This study will be double-blinded. Under normal circumstances, the blind should not be broken. The blind should be broken only if specific emergency treatment would be dictated as knowing the study drug assignment is required for medical management. In such cases, the Investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure in the IWRS. The date, time and reason for the unblinding must be documented in the appropriate field of the electronic case report form (eCRF).

The overall randomization code will be broken only for reporting purposes. This will occur after database lock for the 1st CSR. The unblinded personnel will be pre-defined and documented before breaking the study blind. The study will remain blinded to the investigators, patients and pre-defined blinded personnel from the sponsor and contract research organization until all patients have completed the study and the database has been finalized for study closure.

4.4. Definition of Baseline and Post-Baseline

The baseline value will be considered to be the last non-missing value before the first study drug administration (If there are multiple last non-missing measurements on the same date before the first study drug administration, the result of a scheduled visit will be considered as the baseline value). Post-baseline values will be considered to be all values collected after the first study drug administration.

4.5. External Data Handling

When combining data from eCRF and analytical facilities, discrepancy will be handled as follows:

1) Recorded as sample collected in eCRF but no corresponding results from analytical facility – listing will display only sample collection visit/date from eCRF;

2) No corresponding records in eCRF for results from analytical facility – listing will display only sample collection visit/date and results from analytical facility;

3) Discrepancy in sample collection date from eCRF and analytical facility

    - DXA scan and lateral Spine X-ray: listing will display results, visit and date from analytical facility if not missing; if the date from analytical facility is missing then use the date in eCRF.

- All other measurements: listing will display results from analytical facility and visit/date from eCRF if not missing; if the date is missing in eCRF then use the date from analytical facility.

4.6. Outliers

Any outliers that are detected during the review of the data will be investigated and discussed during the blinded data review meeting (DRM). In general, outliers will not be excluded. Sensitivity analyses and exploratory analyses may be conducted to ensure robustness of study conclusions.

5. ANALYSIS SETS

The following analysis sets are defined: Intent-to-Treat (ITT) set, Full Analysis set (FAS), Per-Protocol set (PPS), PK set, PD set, and Safety set. The following analysis subsets are also defined: ITT–Treatment Period II subset, FAS–Treatment Period II subset, PK–Treatment Period II subset, PD–Treatment Period II subset and Safety–Treatment Period II subset. Analysis sets will be used for the summary of the Treatment Period I (prior to dosing at Week 52). Analysis subsets will be used for the summary of the Treatment Period II (Baseline (if, needed), Week 52 to Week 78).

The treatment groups for Treatment Period I will be ‘CT-P41’ and ‘US-licensed Prolia’. For ITT set, FAS and PPS, the analyses will be performed according to the randomized treatment group. For PK set, PD set and Safety set, the analyses will be performed according to actual treatment group. The actual treatment group will be assigned according to their actual treatment, not according to the randomized treatment, even if there is a discrepancy between the actual treatment and the randomized treatment. If there is a patient with such a discrepancy, patients receiving CT-P41 at least once will be treated as ‘CT-P41’ treatment group. All other patients will be treated as ‘US-licensed Prolia’ treatment group.

The treatment groups for Treatment Period II will be ‘CT-P41 Maintenance’, ‘US-licensed Prolia Maintenance’ and ‘Switched to CT-P41’. For ITT–Treatment Period II subset and FAS–Treatment Period II subset, the analyses will be performed according to the randomized treatment group. For PK–Treatment Period II subset, PD–Treatment Period II subset and Safety–Treatment Period II subset, the analyses will be performed according to actual treatment they received during Treatment Period I and Treatment Period II. The actual treatment group for Treatment Period II subset will be assigned according to their actual treatment received in Treatment Period I and Treatment period II, not according to the randomized treatment, even if there is a discrepancy between the actual treatment and the randomized treatment. If there is a patient with such a discrepancy, the following rules will be applied:

- Patients receiving CT-P41 at least once during Treatment Period I will be treated as ‘CT-P41 Maintenance’ treatment group.

- Patients who receive only US-licensed Prolia during Treatment Period I and receive CT-P41 during Treatment Period II will be treated as ‘Switched to CT-P41’ treatment group.

- Patients who receive only US-licensed Prolia during both Treatment Period I and II will be treated as 'US-licensed Prolia Maintenance' treatment group.

If necessary, the summary of Overall Period will be performed. For the summary of Overall Period, all data collected from patients within each treatment groups of 'CT-P41', 'US-licensed Prolia', 'CT-P41 Maintenance', 'US-licensed Prolia Maintenance' and 'Switched to CT-P41' during the whole study period, regardless of Treatment Period will be summarized. Total count from 'CT-P41' and 'US-licensed Prolia' treatment groups will also be summarized under a 'Total' column. Analysis sets will be used for the summary.

The number of patients in all analysis sets and analysis subsets will be summarized by the treatment group on ITT set and ITT–Treatment Period II subset. A listing will also be provided displaying the analysis sets and analysis subsets on ITT set.

5.1. Intent-to-Treat Set

The ITT set is defined as all patients randomly assigned to receive study drug (CT-P41 or US-licensed Prolia), regardless of whether or not any study drug was administered.

5.1.1. Intent-to-Treat–Treatment Period II Subset

The ITT–Treatment Period II subset is defined as all patients in ITT set who are randomly assigned to receive study drug (CT-P41 or US-licensed Prolia) at Week 52 prior to dosing, regardless of whether or not any study drug was administered.

5.2. Full Analysis Set

The FAS is defined as all patients who receive at least 1 full dose of study drug (CT-P41 or US-licensed Prolia).

5.2.1. Full Analysis set–Treatment Period II Subset

The FAS–Treatment Period II subset is defined as all patients in FAS who receive 1 full dose of study drug (CT-P41 or US-licensed Prolia) at Week 52.

5.3. Per-Protocol Set

The PPS is defined as all patients who receive all 2 doses (full) of study drug (CT-P41 or US-licensed Prolia) at Day 1 (Week 0) and Week 26, and have BMD assessments for lumbar spine at baseline and Week 52. Patients with major protocol deviation that may affect the interpretation of study results of primary efficacy endpoint will be excluded from the PPS. Final determinations of the PPS will be made at the blinded DRM.

5.4. Pharmacokinetic Set

The PK set is defined as all patients who receive at least 1 full dose of study drug (CT-P41 or US-licensed Prolia) and have at least 1 post-treatment PK concentration data with a concentration above the lower limit of quantification (LLoQ) prior to dosing at Week 52. If any patient is found to be non-compliant with respect to dosing, a determination of the PK set will be made on a case-by-case basis at the blinded DRM.

5.4.1. Pharmacokinetic–Treatment Period II Subset

The PK–Treatment Period II subset is defined as all patients in PK set who receive 1 full dose of study drug (CT-P41 or US-licensed Prolia) at Week 52 and have at least 1 post-treatment PK concentration data with a concentration above the LLoQ after Week 52. If any patient is found to be non-compliant with respect to dosing, a determination of the PK–Treatment Period II subset will be made on a case-by-case basis at the blinded DRM.

5.5. Pharmacodynamic Set

The PD set is defined as all patients who receive full dose of study drug (CT-P41 or US-licensed Prolia) at Day 1 (Week 0) and have at least 1 post-treatment PD concentration data with a concentration above the LLoQ prior to dosing at Week 52. If any patient is found to be non-compliant with respect to dosing, a determination of the PD set will be made on a case-by-case basis at the blinded DRM.

5.5.1. Pharmacodynamic–Treatment Period II Subset

The PD–Treatment Period II subset is defined as all patients in PD set who receive 1 full dose of study drug (CT-P41 or US-licensed Prolia) at Week 52 and have at least 1 post-treatment PD concentration data with a concentration above the LLoQ after Week 52. If any patient is found to be non-compliant with respect to dosing, a determination of the PD–Treatment Period II subset will be made on a case-by-case basis at the blinded DRM.

5.6. Safety Set

The Safety set is defined as all patients who receive at least 1 dose (full or partial) of study drug (CT-P41 or US-licensed Prolia).

5.6.1. Safety–Treatment Period II Subset

The Safety–Treatment Period II subset is defined as all patients in Safety set who receive 1 dose (full or partial) of study drug (CT-P41 or US-licensed Prolia) at Week 52.

6. PROTOCOL DEVIATION

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the Institutional Review Board/Independent Ethics Committee and agreed to by the investigator. A major protocol deviation is one that may significantly affect the interpretation of study results or the patient's rights, safety or welfare. CELLTRION will identify major protocol deviation prior to database lock, and it will be discussed during the blinded DRM. Major protocol deviations are defined as follows:

- Mis-randomization (defined as patients who received the opposite treatment to which they were assigned at any timepoint during the study)
- Non-adherence to Inclusion or Exclusion criteria which affect primary result (to be identified through the review of data sourced from the site monitoring database)

- Significant good clinical practice (GCP) non-compliance (sites which have been closed or patients who have been affected due to scientific misconduct and/or serious GCP non-compliance)

- Receiving any prohibited therapy which affect primary result (Section 5.5 of protocol)

Patients with mis-randomization in Treatment Period I will be excluded from PPS, PK set and PD set and corresponding subsets. If mis-randomization occurs for the first time in Treatment Period II, the patients will be excluded from PK–Treatment Period II subset and PD–Treatment Period II subset.

Patients with non-adherence to inclusion or exclusion criteria which affect primary efficacy results will be excluded from PPS.

Patients with significant GCP non-compliance will be excluded from all analysis sets.

Patients receiving any prohibited medication which affect primary results will be excluded from PPS.

The major protocol deviations and other reasons for exclusion from the analysis sets and analysis subsets will be summarized for all patients in ITT set and for ITT–Treatment Period II subset plus randomized patients with a significant GCP non-compliant issue in each Treatment Period. A listing of major/minor protocol deviations discussed during the blinded DRM and other reasons for exclusion from the analysis sets and analysis subsets will also be provided by treatment group for ITT set plus randomized patients with a significant GCP non-compliant issue.

7. PATIENT DISPOSITION

The number of patients who were screened and failed screening will be displayed along with the primary reason for screening failure. A patient will be considered to have screened if the ‘Subject UUID’ was populated in ‘Subject Enrollment’ page of eCRF. A patient will be considered to have failed the screening if the screening failure date is recorded on the ‘Inclusion/Exclusion Criteria’ eCRF page.

The primary reasons for screening failure will be displayed using the following categories:

- Inclusion/Exclusion criteria not met

- Subject withdrew consent

- Other

The number of patients who were randomized, initiated the study treatment, discontinued the study treatment, early terminated the study participation, primary reasons for the study treatment discontinuation and primary reasons for the early termination of study participation in each treatment period will be displayed for the ITT set and ITT–Treatment Period II subset

along with percentage by treatment group. The number and percentage of patients who complete the study treatment and the study participation will also be displayed in Treatment Period II.

Patient disposition will be defined as follows:

- Randomized: A patient will be considered to have been randomized in each treatment period if a randomization ID is recorded on 'Randomization' eCRF page at Day 1 (Week 0) for Treatment Period I and Week 52 for Treatment Period II.

- Initiated the study treatment: A patient will be considered to have initiated the study treatment in each treatment period if it is recorded as 'Yes' to 'Was study drug administered?' on 'Study Drug Administration' eCRF page at Day 1 (Week 0) for Treatment Period I and Week 52 for Treatment Period II.

- Discontinued the study treatment: A patient will be considered to have discontinued the study treatment if it is recorded as 'No' to 'Did the subject complete the treatment?' on 'Study Treatment Termination' eCRF page. If the patient has a 2nd randomization ID, the patient will be considered to have discontinued in the Treatment Period II, whereas the patient without a 2nd randomization ID will be considered to have discontinued the study treatment in Treatment Period I.

- Early terminated the study participation: A patient will be considered to have terminated the study participation early if it is recorded as 'No' to 'Did the subject complete the study? (up to Week 78)' on 'End of Study Participation' eCRF page. If the patient has a 2nd randomization ID, the patient will be considered to have terminated the study participation in the Treatment Period II, whereas the patient without a 2nd randomization ID will be considered to have terminated the study participation in Treatment Period I.

- Completed the study treatment: A patient will be considered to have completed the study treatment if it is recorded as 'Yes' to 'Did the subject complete the treatment?' on 'Study Treatment Termination' eCRF page.

- Ongoing: A patient will be considered to be ongoing if the patient is randomized and recorded nothing to 'Did the subject complete the study? (up to Week 78)' on 'End of Study participation' eCRF page.

- Completed the study participation: A patient will be considered to have completed the study if it is recorded as 'Yes' to 'Did the subject complete the study? (up to Week 78)' on 'End of Study participation' eCRF page.

In addition, time on the study treatment prior to discontinuation will also be summarized, for those patients who initiate the study treatment and prematurely discontinue the treatment for ITT set and for ITT–Treatment Period II subset by treatment group. Time on the study treatment (days) will be calculated as (date of the last administration–date of the first administration+1).

Patient disposition data will be listed for the ITT set by treatment group. A separate listing of patients reported as screening failures will be provided.

8. DEMOGRAPHICS, DISEASE CHARACTERISTICS AND BACKGROUND CHARACTERISTICS

Demographics, stratification details, disease characteristics and background characteristics will be summarized on ITT set unless otherwise specified. Also, all data will be listed for ITT set.

8.1. Demographics and Stratification Factors

The demographic measures (including age, ethnicity and race), height, weight, body mass index (kg/m^2) at screening and stratification factors for first randomization (age group, baseline BMD T-score for lumbar spine and prior bisphosphonates therapy) will be summarized on ITT set. In addition, the stratification factor for second randomization (change from baseline in BMD for lumbar spine at Week 52) will be summarized on ITT–Treatment Period II subset. If there is a discrepancy between IWRS and eCRF in the stratification factors, the factors will be summarized using the final data collected on the eCRF.

The demographic measures at screening and stratification factors will be listed by treatment group.

8.2. Disease Characteristics

The following disease characteristics will be summarized by treatment group: vertebral fracture (number of patients with at least one vertebral fracture at baseline, site of fracture (T4 to L4) and Genant semi-quantitative grade of vertebral fracture at baseline based on lateral spine X-ray), nonvertebral fracture (number of patients with at least one nonvertebral fracture, site of fracture, trauma severity and surgery history based on eCRF ‘Disease Characteristic’ page), baseline BMD T-score of lumbar spine, total hip and femoral neck based on DXA scan, years since menopause and smoking history.

The disease characteristics will be listed by treatment group showing the details of disease characteristics.

8.3. Viral Serology

The following viral serology assessments will be performed at the time points specified in the schedule of assessments (Appendix 16.1):

- Hepatitis B Surface Antigen (HBsAg)
- Hepatitis B Surface Antibody (HBsAb)
- Hepatitis B Core Antibody (HbcAb) (IgM)
- Hepatitis C Antibody

- Human Immunodeficiency Virus (HIV)
- Hepatitis B e antibody (HbeAb, if necessary)
- Hepatitis B e antigen (HbeAg, if necessary)
- Hepatitis B virus (HBV) Deoxyribonucleic Acid (DNA) (if necessary)
- Hepatitis C virus (HCV) RiboNucleic Acid (RNA) (if necessary)

If there is confirmatory test result, the confirmatory result for HBsAg and HIV will be used instead of the initial test result in the table summary.

Viral serology results at baseline will be summarized by parameters and treatment group. All viral serology results will be listed by treatment group.

8.4. Follicle-stimulating Hormone

At screening, blood sampling for Follicle-stimulating hormone (FSH) assessment will be performed in order to confirm menopause (central laboratory).

The FSH results will be listed by treatment group.

8.5. New York Heart Association Functional Classification

At screening, the New York Heart Association (NYHA) functional classification assessment will be performed. The NYHA functional classification is used in patients with history of heart failure with score running from I to IV. The criteria for heart failure are defined as Table 1 (Zhang *et al*., 2018):

Table 1. New York Heart Association Functional Classification

Class	Symptoms
I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II (Mild)	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III (Moderate)	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea.
IV (Severe)	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

The NYHA criteria assessment data will be listed by treatment group.

8.6. Medical History

Medical history will be captured at screening and will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 24.0 or higher). Medical history will be summarized by treatment group, system organ class (SOC) and preferred term (PT) along with the total number of medical histories and the number and percentage of patients with at least one medical history. Medical history will be listed by treatment group.

8.7. Inclusion and Exclusion Criteria

Details of inclusion and exclusion criteria can be found in Sections 4.1.1 and 4.1.2 of the protocol. Non-adherence to inclusion/exclusion criteria will be listed by treatment group.

8.8. General Comments

Data collected on the 'General Comments' eCRF page will be presented in a listing. Comments related to COVID-19 will be flagged.

8.9. War in Ukraine

All patients whose trial participation is impacted by War in Ukraine discussed during the blinded DRM will be presented with details of the impact in a listing.

8.10. COVID-19

A listing of patients whose trial participation is impacted by COVID-19 with details of the impact, will be prepared, if applicable.

9. MEDICATIONS AND TREATMENTS

All details of prior and concomitant medication and study drug administered for both Treatment Period I and II will be summarized on Safety set and Safety–Treatment Period II subset unless otherwise specified. Also, all data including co-administration of calcium and vitamin D will be presented in a listing in Safety set.

9.1. Prior and Concomitant Medications

All medications taken within 30 days prior to the signed date of Informed Consent Form (ICF) and until the EOS visit will be recorded in the patient's eCRF. All medications will be coded according to the World Health Organization (WHO) drug dictionary version March 2021 or the later.

Medications will be classified as either prior or concomitant.

A prior medication is defined as any medication where the start and stop dates are before the date of the first study drug administration. It will be classified as follows:

- A medication checked as 'yes' to 'If stop date is unknown, was this drug stopped before the first administration of study drug?' on 'Prior & Concomitant Medications' eCRF page (date imputation is not necessary), or

- A medication having stop date (recorded or imputed) before the first study drug administration date

A concomitant medication is defined as any medication that has a stop date (recorded or imputed) on or after the date of the first study drug administration or missing, and any medication not classified as a prior medication will be classified as a concomitant medication. Also, a concomitant medication will be classified as Treatment Period I or Treatment Period II, defined as follows:

- Treatment Period I: a concomitant medication with a start date (recorded or imputed) prior to the study drug administration in Treatment Period II, or a concomitant medication for a patient who did not enter Treatment Period II will be included.

- Treatment Period II: a concomitant medication with a start date (recorded or imputed) on or after the date of study drug administration in Treatment Period II will be included.

To classify the medication as prior or concomitant and to determine the Treatment Period (I or II) of a concomitant medication, incomplete medication start/stop dates will be imputed as follows:

If the stop date is incomplete, the following rules will be applied:

- Missing day: Assume the last day of the month.

- Missing day and month: Assume December 31st.

- Missing day, month and year: Leave it as missing.

In the case of the death of a patient, and the imputed stop date is after the date of death, the stop date will be imputed as the date of death.

If the start date is incomplete, the following rules will be applied. If the stop date is incomplete, imputed stop date will be used instead of recorded stop date:

- Missing day (e.g. XXFEB2023): the month and year of the partial date will be compared to the date of the first study drug administration.

    - If the month and the year are equal for both dates, the start date will be imputed as the earlier date of: (i) the date of the first study drug administration, or (ii) the recorded/imputed stop date of the medication. If the recorded/imputed stop date is missing, the start date will be imputed as the first study drug administration.

    - If the month or the year are not equal for both dates, the start date will be imputed as the first day of the month (e.g. 01FEB2023).

- Missing day and month (e.g. XXXX2023): the year of the partial date will be compared

to the date of the first study drug administration.

- If the years of both dates are equal, the start date will be imputed as the earlier date of: (i) the date of the first study drug administration, or (ii) the recorded/imputed stop date of the medication. If the recorded/imputed stop date is missing, the start date will be imputed as the first study drug administration.

- If the years are not equal for both dates, the start date will be imputed as the first day of January of the year (e.g. 01JAN2023).

- Missing day, month and year (e.g. XXXXXXXX): the start date will be imputed as the earlier date of: (i) the date of the first study drug administration, or (ii) the recorded/imputed stop date of the medication. If the recorded/imputed stop date is missing, the start date will be imputed as the date of the first study drug administration.

The prior medications will be summarized by treatment group, drug class (using Anatomical Therapeutic Chemical [ATC] level 2 (if missing, ATC level 1)) and PT along with the total number of prior medications and the number and percentage of patients with at least one prior medication. The summary will be performed in the Safety set.

The separate table will be also generated for the concomitant medications by treatment period, treatment group, drug class, and PT along with the total number of concomitant medications and the number and percentage of patients with at least one concomitant medication. The summaries of concomitant medications will be generated for Treatment Period I, Treatment Period II and Overall Period, separately. The Overall Period summary will be performed in the safety set using the columns of ‘CT-P41’, ‘US-licensed Prolia’, ‘CT-P41 Maintenance’, ‘US-licensed Prolia Maintenance’, ‘Switched to CT-P41’ and ‘Total’.

A listing for prior and concomitant medications will be provided by treatment group.

9.1.1. Co-administration of Calcium and Vitamin D

Data on co-administration of calcium and vitamin D will be collected separately from all other medications.

A listing will be provided by treatment group showing the details of co-administration of calcium and vitamin D.

9.2. Exposure to Study Drug

The following information will be included in summary of study drug administration at each scheduled visit:

- the number and percentage of patients with dose administered

- the number and percentage of patients who did and did not have whole volume of study drug administered successfully

- the number and percentage of patients corresponding to each reason why the dose was not administered

In addition, the total number of doses received will be summarized for Overall Period. The Overall Period summary will be performed in the Safety set using the columns of 'CT-P41', 'US-licensed Prolia', 'CT-P41 Maintenance', 'US-licensed Prolia Maintenance', 'Switched to CT-P41' and 'Total'. A listing will be provided by treatment group showing the details of study drug administration.

10. EFFICACY ANALYSES

The percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA (analyzed by central imaging vendor) at Week 52 is the primary efficacy endpoint.

The secondary efficacy endpoints are as below:

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

The percent change from baseline for BMD at each visit will be calculated as ([Result at each visit – Result at Baseline] / Result at Baseline) × 100.

The primary efficacy endpoint analysis will be conducted using FAS. A supportive analysis will be conducted in PPS. In addition, FAS will be used for a sensitivity analysis to evaluate the impact of missing data on the primary efficacy analysis result.

For secondary efficacy endpoints, FAS and PPS will be used for summaries of Treatment Period I data and FAS–Treatment Period II subset will be used for summaries of Treatment Period II data.

All efficacy listings will be based on the ITT set.

10.1. Primary analysis

The analysis of the primary efficacy endpoint (percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52) will be conducted on the FAS using an analysis of covariance (ANCOVA) model coupled with multiple imputation (MI) assuming the data to be missing at random (MAR). The ANCOVA model will include the treatment as a fixed effect and age, baseline BMD T-score at the lumbar spine and prior bisphosphonates therapy (Yes versus No) as covariates using [redacted]. Also ANCOVA will be conducted on the PPS as supportive analysis for the primary efficacy endpoint.

Multiple imputation with the MAR assumption will be applied using [redacted] The multiple imputed datasets will be generated based on linear regression models on percent change from baseline in BMD for lumbar spine at Week 52 with treatment group, age, baseline BMD T-score at the lumbar spine and prior bisphosphonates therapy (Yes versus No) as covariates. Ten imputed datasets will be generated. ANCOVA will be performed on each of the 10 multiple imputed datasets. The results from each set of imputed datasets will then be

pooled using [redacted], aggregating the results for the final statistical inference using Rubin's method.

As a result, a point estimate and its 90% confidence interval (CI) for the difference in the mean of the primary endpoint between CT-P41 treatment group and US-licensed Prolia treatment group will be produced. Therapeutic equivalence of clinical efficacy will be concluded if the 90% CI for the treatment difference is entirely within − 1.45% to + 1.45%.

10.1.1. Sensitivity Analysis for Primary Efficacy Endpoint

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

First, under MAR assumption, missing percent change from baseline in BMD for lumbar spine at Week 52 will be imputed by MI method. A point estimate and its 90% CI for treatment difference will be provided using an ANCOVA in the same way as the primary analysis.

Then, a tipping point analysis will be performed to evaluate the impact of missing data under MNAR scenario. For the imputed cases by the above method under MAR scenario percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52 will be shifted gradually in each treatment group. A point estimate and its 90% CI will be provided for each scenario. The gradual shift will be made until when the 90% CI is no longer entirely within the therapeutic equivalence margin of ±1.45%.

In addition to the tipping point analysis, imputation under a non-inferiority (NI) null hypothesis and non-superiority null hypothesis (Koch, 2008) will be performed as a part of sensitivity analysis. The percent change from baseline imputed by the MI will be further adjusted by the NI or non-superiority margin for the CT-P41 treatment group (± 1.45%), when testing NI or non-superiority hypothesis, respectively. In agreement with FDA, this method will be applied only to the patients outside Ukraine in CT-P41 treatment group. For the others, the imputed values are not adjusted so the initial imputed values remain the same.

10.1.2. Subgroup Analysis by Age

To assess the consistency of the primary efficacy endpoint by age subgroup (<65, >=65), actual value and percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52 will be summarized using descriptive statistics including 95% CI for the mean by each treatment group in each subgroup in the FAS.

10.2. Secondary analysis

10.2.1. Bone Mineral Density by Dual-energy X-ray absorptiometry

Actual value and percent change from baseline in BMD for lumbar spine (L1 to L4), total hip and femoral neck by DXA will be summarized using descriptive statistics by treatment group, anatomical site and visit.

A listing will be provided by treatment group showing the details of BMD by DXA.

10.2.2. Incidence of Fractures

The vertebral, nonvertebral and hip fractures during the study will be assessed.

The vertebral fracture will be assessed by semi-quantitative grading by lateral spine X-ray at a central imaging vendor (Genant *et al*., 1993) as follows:

- Grade 0=no fracture
- Grade 1=mild fracture, 20 – 25% reduction in vertebral height (anterior, middle, or posterior)
- Grade 2=moderate fracture, 25 – 40% reduction in any height
- Grade 3=severe fracture, greater than 40% reduction in any height

The semi-quantitative grade of the vertebral fracture will be summarized in a shift table to detect changes from baseline.

The new vertebral fracture by each vertebra (T4 to L4) is defined as an increase of at least one grade in the vertebra that was normal (Grade 0) at baseline (Cummings *et al*., 2009). The summary of new vertebral fractures by Treatment Period will be performed for the case when an increase of the grade occurs for the first time in each treatment period.

The nonvertebral fracture as secondary efficacy endpoint includes fractures other than those of the vertebra, excluding pathologic fractures and fractures of the skull, facial bones, mandible, metacarpals, and phalanges of fingers or toes as they are not associated with decreased BMD. The nonvertebral fracture endpoint will also exclude if they are associated with severe trauma as a fall from a height higher than a stool, chair, or first rung of a ladder or severe trauma other than a fall.

Among the nonvertebral fractures as secondary efficacy endpoint, hip fractures are those occurring at the site of femur neck, femur intertrochanter, or femur subtrochanter.

Final determinations of the nonvertebral fractures as secondary efficacy endpoint will be made at the blinded DRM.

The results of scheduled visits for new vertebral fracture (assessed by lateral spine X-ray) will be classified as Treatment Period I or II by Week 52 (Treatment Period I for the data up to Week 52, otherwise Treatment Period II). On the other hand, the results of unscheduled visits for new vertebral (assessed by lateral spine X-ray or other radiographs and/or radiology or medical report), nonvertebral and hip fractures (assessed by radiographs and/or radiology or medical report) will be classified as Treatment Period I and II by following rules:

- Treatment Period I: Fractures with an assessment date on or before the date of study drug administration in Treatment Period II, or fractures for patients who did not enter Treatment Period II will be included.
- Treatment Period II: Fractures with an assessment date after the date of study drug administration in Treatment Period II will be included.

Incidences of new vertebral fracture, nonvertebral fracture and hip fracture will be summarized by treatment group and site of fracture. The fracture summary will be generated for Treatment Period I, Treatment Period II and Overall Period, separately. The Overall Period summary will be performed in the FAS using the columns of 'CT-P41', 'US-licensed Prolia', 'CT-P41 Maintenance', 'US-licensed Prolia Maintenance' and 'Switched to CT-P41'.

A listing of semi-quantitative grade of vertebral fractures (T4 to L4) based on lateral spine X-ray or other radiographs and/or radiology or medical report will be provided by treatment group. Also, a listing of detailed information of nonvertebral and hip fractures as secondary efficacy endpoint based on radiographs and/or radiology or medical report will be provided by treatment group.

10.2.3. Quality of Life Assessment

Changes in the health-related quality of life from baseline will be assessed using osteoporosis assessment questionnaire short version (OPAQ-SV) and EuroQoL-5 Dimensions-5 Levels health survey (EQ-5D-5L) at the time points specified in the schedule of assessments (Appendix 16.1).

10.2.3.1. Osteoporosis Assessment Questionnaire Short Version

The OPAQ-SV (English (US) version 2.2) contains 34 questions that can be summarized into 7 domains (walking/bending, daily activities, transfer, fear of falls, body image, independence and back pain) and 3 dimensions (physical function, emotional status, and back pain).

Table 2. Question Mapping of OPAQ-SV

Dimension	Domain	Questions
Physical function	Walking/bending	1 – 7
	Daily activities	8 – 15
	Transfer	16 – 19
Emotional status	Fear of falls	20 – 24
	Body image	29 – 31
	Independence	32 – 34
Back pain	Back pain	25 – 28

Dimension scores will be calculated as per following logic:

1. Standardize the response for each question to a value (0, 25, 50, 75, 100) according to the Table 3.

2. Average the standardized value within each dimension to create dimension scores. Calculate each dimension score only if ≥50% of the questions in each dimension were completed. Otherwise, the dimension score is set as missing. (e.g. physical

function dimension: question of 1 to 19; Calculate the score if ≥10 items were completed; otherwise set the score as missing.)

Table 3. Scoring System of OPAQ-SV

Question Number	Question Response	Standardized Value
2, 5, 6, 7, 16 – 19, 25, 27, 28	All days Most days Some days Few days No days	0 25 50 75 100
1, 3, 4, 8, 9, 10	All days Most days Some days Few days No days	100 75 50 25 0
11, 12, 20, 21, 22, 23, 24, 29, 30, 31, 33, 34	Always Very often Sometimes Almost never Never	0 25 50 75 100
13, 14, 15, 32	Always Very often Sometimes Almost never Never	100 75 50 25 0
26	Severe Moderate Mild Very mild None	0 25 50 75 100

Actual value and change from baseline of dimension scores will be summarized using descriptive statistics by treatment group, dimension and visit. All data of OPAQ-SV will be listed by treatment group and visit.

10.2.3.2. EuroQoL-5 Dimensions-5 Levels Health Survey

The EQ-5D-5L (Self-Complete UK version 1.2) consists of the EQ-5D descriptive system and

EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system is a preference-based measurement across 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with 5 levels (no problem, slight problem, moderate problem, severe problem and extreme problem/unable to) within each dimension.

The EQ-5D-5L descriptive system will be summarized by a single summary number (index value), which reflects how good or bad a health state is (with higher scores indicating higher health state) using United States value set (Pickard *et al*., 2019). The data from five dimensions will be used to calculate a single index value using United States value set according to Table 4.

The EQ-5D index value will be calculated as per following logic:

1. Match the question responses to values according to Table 4. For example, if the question response is 'Slight problem' in mobility dimension, then the value is 0.096.

2. Index value will be calculated as 1 – (mobility value + self-care value + usual activities value + pain/discomfort value + anxiety/depression value). The index value will only be calculated if all question responses are recorded.

Table 4. Scoring System of EQ-5D Descriptive System (United States Value Set)

Dimension	Question Response	Value
Mobility	No problem	0
	Slight problem	0.096
	Moderate problem	0.122
	Severe problem	0.237
	Unable	0.322
Self-care	No problem	0
	Slight problem	0.089
	Moderate problem	0.107
	Severe problem	0.220
	Unable	0.261
Usual activities	No problem	0
	Slight problem	0.068
	Moderate problem	0.101
	Severe problem	0.255
	Unable	0.255
Pain/discomfort	No pain	0
	Slight pain	0.060
	Moderate pain	0.098
	Severe pain	0.318

	Extreme pain	0.414
Anxiety/depression	Not anxious	0
	Slightly anxious	0.057
	Moderately anxious	0.123
	Severely anxious	0.299
	Extremely anxious	0.321

Also, EQ VAS measures the self-rated health on a vertical visual analogue scale requiring patients to directly rate their current health. 0 means the worst health and 100 means the best health a patient can imagine.

Actual value and change from baseline of EQ-5D index value and EQ VAS will be summarized using descriptive statistics by treatment group and visit.

All data for EQ-5D-5L will be listed by treatment group and visit.

11. PHARMACOKINETIC ANALYSES

Blood samples for PK analyses (central laboratory) will be obtained according to Appendix 16.1. The PK parameters will be calculated by non-compartmental analysis method from the concentration-time data. Actual sampling time relative to dosing will be used in the calculation of all derived PK parameters. For patients who early discontinue the study treatment, PK samples will be collected until the next scheduled study drug administration visit. The samples and PK parameter results collected after the next scheduled study drug administration visit will be flagged in the listing but excluded from the table.

Pharmacokinetic analyses for Treatment Period I will be performed in PK set and PK analyses for Treatment Period II will be performed in PK–Treatment Period II subset, unless otherwise specified. Serum concentration of Denosumab will be listed by treatment group for the Safety set and all data for the PK parameters will be listed by treatment group for the PK set.

All serum concentration below the LLoQ will be set to 0 in the descriptive summaries of serum concentration and PK parameter estimation.

11.1. Serum Concentrations

Serum concentrations of Denosumab will be summarized by treatment group and visit using descriptive statistics: n, mean, SD, geometric mean, CV (%), minimum, median and maximum.

Serum concentrations of Denosumab will be presented in a listing by treatment group and the values below the LLoQ will be indicated. Mean serum concentration time profiles will be plotted by treatment group on linear and semilogarithmic scales based on scheduled sampling times.

11.2. Pharmacokinetic Parameters

- Maximum serum concentration (C_{max}) after the first administration of study drug (over the initial 6 months [26 weeks])
- Trough serum concentration (C_{trough}) (concentration prior to the next study drug administration up to Week 78)

PK parameters will be summarized by treatment group and visit using descriptive statistics: n, mean, SD, geometric mean, CV (%), minimum, median and maximum. All data for the PK parameters will be listed by treatment group.

12. PHARMACODYNAMIC ANALYSES

Blood samples for PD analyses (central laboratory) will be obtained according to Appendix 16.1. The PD parameters will be calculated by non-compartmental analysis method from the concentration-time data. Actual sampling time relative to dosing and all samples up to and including Week 26 for all patients will be used in the calculation of AUEC (Area under the Effect Curve). For patients who early discontinue the study treatment, PD samples will be collected until the next scheduled study drug administration visit. The samples collected after the next scheduled study drug administration visit will be flagged in the listing but excluded from the table.

Serum concentration below the LLoQ will be set to the LLoQ and the value above the upper limit of quantification (ULoQ) will be set to the ULoQ for the descriptive summaries of PD concentration and PD parameter estimation.

The AUEC and the rebounded area will be calculated using absolute percent change from baseline and the linear trapezoidal rule. The percent change from baseline will be calculated as ([Concentration at each timepoint – Concentration at baseline] / Concentration at baseline) × 100. The absolute percent change from baseline will be taken as the derived percent change from baseline regardless of a positive or negative change. The rebound area which is a positive percent change from baseline will be set to 0. For patients who do not have serum concentration result of serum carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX)/Procollagen Type 1 N-terminal Propeptide (P1NP) at Week 26, AUEC of s-CTX/P1NP will be flagged in the listing but excluded from the table.

The PD analyses for Treatment Period I will be performed in PD set and the analyses for Treatment Period II will be performed in PD–Treatment Period II subset, unless otherwise specified. Also, all PD data will be listed in ITT set.

12.1. Serum concentration of s-CTX and P1NP

Actual value and percent change from baseline of serum concentrations of s-CTX and P1NP will be summarized by treatment group and visit according to Appendix 16.1 using descriptive statistics: n, mean, SD, geometric mean, CV (%), minimum, Q1 (the first quartile), median, Q3 (the third quartile) and maximum. Geometric mean and CV (%) will not be presented for change from baseline summary.

The percent change from baseline for serum concentration at each visit will be calculated as

([Result at each visit – Result at Baseline] / Result at Baseline) × 100.

A listing will be provided by treatment group and visit showing serum concentrations of s-CTX and P1NP. Percent change from baseline of serum concentrations of s-CTX and P1NP time profiles will be plotted by treatment group on linear scale based on scheduled sampling times. Median, Q1 (the first quartile) and Q3 (the third quartile) will be presented in the figure.

12.2. AUEC of s-CTX and P1NP

AUEC of s-CTX and P1NP over the initial 6 months (from Day 1 predose to Week 26 predose) will be summarized by treatment group using descriptive statistics: n, mean, SD, geometric mean, CV (%), minimum, median and maximum.

A listing will be provided by treatment group and visit showing AUEC of s-CTX and P1NP.

13. SAFETY ANALYSES

Safety analyses will include AEs, clinical laboratory test (hematology, clinical chemistry, urinalysis and microscopic urinalysis), vital signs and weight, electrocardiograms (ECGs), physical examination, local site pain, hypersensitivity/allergic reaction monitoring and immunogenicity.

All safety analyses for Treatment Period I will be performed in the Safety set and safety analyses for Treatment Period II will be performed in the Safety–Treatment Period II subset, unless otherwise specified. Also, all safety data will be listed by treatment group in the Safety set.

13.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient enrolled into this study by signing the ‘Informed Consent’ eCRF page, regardless of its causal relationship to study drug.

All AEs will be classified by SOC and PT according to the MedDRA version 24.0 or higher. AEs will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

A treatment-emergent adverse event (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in severity or frequency after exposure to study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

TEAEs will be classified and summarized for Treatment Period I and Treatment Period II, defined as follows:

- Treatment Period I: TEAEs with a start date (recorded or imputed) prior to the study drug administration in Treatment Period II, or TEAEs for patients who did not enter Treatment Period II will be included.

- Treatment Period II: TEAEs with a start date (recorded or imputed) on or after the date of study drug administration in Treatment Period II will be included.

To determine whether the event is a TEAE and to classify the Treatment Period (I or II), the incomplete start/stop dates of an AE will be imputed as follows:

If the stop date is incomplete, the following rules will be applied.

- Missing day: Assume the last day of the month.
- Missing day and month: Assume December 31st.
- Missing day, month and year: Leave it as missing.

In the case of the death of a patient, the stop date will be imputed as the date of death if the imputed stop date is after the date of death.

If the start date is incomplete, the following rules will be applied. If the stop date of the AE is incomplete, imputed stop date will be used instead of recorded stop date.

- Missing day (e.g. XXFEB2023): the month and year of the partial date will be compared to the date of the first study drug administration.
    - If the month and year are equal for both dates, the AE start date will be imputed as the earlier date of: (i) the date of the first study drug administration, and (ii) the stop date of the AE. If the AE stop date is missing (e.g. XXXXXXXXX), the AE start date will be imputed as the date of the first study drug administration.
    - If the month or year are not equal, the AE start date will be imputed as the first day of the month (e.g. 01FEB2023).
- Missing day and month (e.g. XXXXX2023): the year of the partial date will be compared to the date of the first study drug administration.
    - If the years of both dates are equal, start date will be imputed as the earlier date of: (i) the date of the first study drug administration, and (ii) the stop date of the AE. If the AE stop date is missing (e.g. XXXXXXXXX), the AE start date will be imputed as the date of the first study drug administration.
    - If the years are not equal, start date will be imputed as the 1st of January of the partial date year (e.g. 01JAN2023).

If the AE start date is missing (e.g. XXXXXXXXX), start date will be imputed as the earlier date of: (i) the date of the first study drug administration, and (ii) the stop date of the AE. If the AE stop date is missing (e.g. XXXXXXXXX), the AE start date will be imputed as the date of the first study drug administration.

In table summaries, TEAEs will be considered to be related if relationship is possible, probable or definite for the study treatment. If relationship or severity is missing, it will be summarized separately under a missing category.

A listing will be provided by treatment group showing the details of AEs.

13.1.1. Treatment-Emergent Adverse Events

The TEAEs during the study will be summarized by treatment group, SOC, PT, relationship and severity, displaying the number and percentage of patients with at least one TEAE using only the worst severity recorded at each level of summarization. The total number of events and number of patients with at least one TEAE will also be displayed.

The TEAEs by treatment group, SOC, PT, severity (regardless of relationship) will also be summarized.

In addition, the TEAEs summary with PT reported for at least 3% of patients in either treatment group will be summarized separately.

The TEAE summaries will be generated for Treatment Period I, Treatment Period II and Overall period, separately. The overall period summary will be performed in the safety set using the columns of 'CT-P41', 'US-licensed Prolia', 'CT-P41 Maintenance', 'US-licensed Prolia Maintenance', 'Switched to CT-P41' and 'Total'.

The summary of TEAEs will be presented in alphabetical order of SOC. Within each SOC, the PTs will be also presented in alphabetical order.

13.1.2. Serious Adverse Events

A serious adverse event (SAE) is defined as any event that is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or results in death. Important medical events that may not be life threatening, result in death, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Treatment-emergent serious adverse events (TESAEs) will be summarized by treatment group, SOC, PT, relationship and severity in a same manner as the table of TEAEs described in Section 13.1.1. In addition, TESAEs will be summarized by treatment group, SOC, PT, relationship and serious criteria, displaying the number and percentage of patients with at least one TESAE using only the most severe SAE recorded at each level of summarization. The total number of events and number of patients with at least one TESAE will also be displayed.

A listing will be provided by treatment group showing the details of SAEs. Also, an additional listing for serious criteria and SAE description will be provided by treatment group.

13.1.3. Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation

All patients who have a TEAE with an action taken with study drug of "Drug Withdrawn" will be summarized by treatment group, SOC, PT, relationship and severity in a same manner as the table of TEAEs described in Section 13.1.1.

A listing will be provided by treatment group showing the details of TEAEs leading to study drug discontinuation.

13.1.4. Adverse Events Leading to Death

All patients who have a SAE with serious criteria of "Death" will be presented. Time to death from the first/last study drug administration will be calculated as (date of death-date of the first/last study drug administration+1).

A listing will be provided by treatment group showing the details of TEAEs leading to death.

13.1.5. Treatment-Emergent Adverse Events of Special Interest

The TEAEs of special interest are as following:

- Injection site reaction (ISR): TEAEs classified as ISR in the eCRF ('Yes' to 'Is adverse event classified as an Injection Site Reaction?' on 'Adverse Event' eCRF page) will be included.
- Drug-related hypersensitivity/allergic reactions: TEAEs classified as Drug-related Hypersensitivity/allergic reactions in the eCRF ('Yes' to 'Is adverse event classified as Drug-related Hypersensitivity/allergic reactions?' on 'Adverse Event' eCRF page) will be included.
- Infection: TEAEs coded with a SOC of 'Infections and Infestations' will be included.
- Hypocalcaemia: TEAEs coded with a PT of 'Hypocalcaemia' or 'Hypocalcaemic seizure' will be included.
- Osteonecrosis of the jaw: TEAEs coded with a PT of 'Osteonecrosis of jaw' will be included.
- Atypical femoral fracture: TEAEs coded with a PT of 'Atypical femur fracture' will be included.
- Dermatologic reactions: TEAEs coded with a high level group term (HLGT) of 'Epidermal and dermal conditions' will be included.

The TEAEs of special interest will be summarized by treatment group, SOC, PT, relationship and severity in a same manner as the table of TEAEs described in the first paragraph of Section 13.1.1. In addition, tables for signs and symptoms regarding Drug-related hypersensitivity/allergic reactions and ISR will be provided by SOC, PT and severity.

A listing will be provided showing the details of TEAEs of special interest. Also, listings including additional information for TEAEs classified as Drug-related hypersensitivity/allergic reactions and ISR will be provided by treatment group, respectively. In addition, a listing for atypical femoral fracture analyzed by central imaging vendor will be provided.

13.1.6. Treatment-Emergent Adverse Events of Fracture

The TEAEs classified as a fracture ('Yes' to 'Was Event Fracture' on 'Adverse Event' eCRF page) will be included in the table summary of TEAEs described in the first paragraph of Section 13.1.1. The TEAEs classified as a fracture in the eCRF will be presented in a listing by treatment group showing the details of fracture.

Also, a listing of detailed information of vertebral (except for T4-L4) and nonvertebral fractures including atypical femoral fracture based on radiographs and/or radiology or medical report will be provided by treatment group.

13.2. Clinical Laboratory Evaluations

Blood and urine samples for clinical laboratory assessments will be collected at the time points specified in the schedule of assessments (Appendix 16.1) and analyzed at the central laboratory. However, the samples from subjects of Ukraine will be analyzed in [redacted] laboratory after the outbreak of the war in Ukraine.

In order to determine the study drug administration at Weeks 26 and 52, the tests for serum 25-OH vitamin D, albumin-adjusted total serum calcium, total calcium, serum albumin, phosphate and magnesium will be performed at the local laboratory at first and then analyzed at the central laboratory. The parameters analyzed at the local laboratory to determine the study drug administration and the parameters analyzed only from the central laboratory not in [redacted] laboratory will be displayed in the listing but excluded from the table.

For laboratory parameters with numeric results, actual values and change from baseline will be summarized using descriptive statistics by treatment group, laboratory category (clinical chemistry, hematology and urinalysis (except for microscopic examination)), test parameter and visit.

Some numeric parameters will be labeled with a CTCAE term and grading will be applied to post-baseline values for the parameters where possible according to CTCAE version 5.0. Grades that require clinical input only will not be assigned to these parameters. Grades whose criteria consist of part numeric and part clinical input will be assigned based on the numeric portion only. The CTCAE terms and ranges for applicable parameters are listed in Appendix 16.2. The CTCAE grades will be Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) and Grade 4 (Life-threatening). The CTCAE Grade 5 (Death) will not be applied in this analysis since death cannot be determined from a numeric laboratory result. If the post-baseline result for a patient does not satisfy any CTCAE grade, it will be classified as "No grade". The number and percentage of patients will be summarized by treatment group, laboratory category, CTCAE term, visit and grade. In addition, CTCAE grading of albumin-adjusted total serum calcium of [redacted] laboratory will be performed according to lab normal range of central laboratory because the corresponding normal range does not exist. Additional table will be generated using the most severe grade after the first study drug administration for each Treatment Period and Overall Period. The most severe grade will be selected considering all post-baseline scheduled and unscheduled visits.

The results of scheduled visits for laboratory results will be classified as Treatment Period I or II by Week 52 (Treatment Period I for the data up to Week 52, otherwise Treatment Period II).

On the other hand, the results of unscheduled visits for laboratory results will be classified as Treatment Period I and II by the following rules:

- Treatment Period I: Laboratory results with an assessment date on or before the study drug administration in Treatment Period II, or the results for patients who did not enter Treatment Period II will be included.
- Treatment Period II: Laboratory results with an assessment date after the date of study drug administration in Treatment Period II will be included.

Categorical parameters of urinalysis (except for microscopic examination) will be labeled with "Normal" or "Abnormal" by central laboratory and coded to the category ("Normal" or "Abnormal") according to Table 5 only for [redacted] laboratory. The parameters will be summarized in a shift table from baseline by each scheduled visit. The number and percentage of patients will be displayed for post-baseline visits by treatment group, test parameter and visit.

Table 5. Normal Criteria for Categorical Laboratory Urinalysis Parameters

Tests	Normal	Abnormal
Color	Light yellow, Yellow, Straw	Red, Orange, Greenish, Colorless, etc.
Glucose	Not found	+/-, 1+, 2+, 3+
Protein	Not found	+/-, 1+, 2+, 3+, 4+
Bilirubin	Not found	1+, 2+, 3+
Occult Blood	Not found	1+, 2+, 3+
Ketones	Not found	+/-, 1+, 2+, 3+
Nitrites	Not found	1+
Leukocyte	Not found	+/-, 1+, 2+, 3+, 4+

"+/-" is identical to "trace"

All clinical chemistry, hematology and urinalysis data including microscopic examination will be presented in the separate listings including CTCAE term, grade and high and low flags to show if a value was outside the normal range, if applicable. The summaries and listings will be based on the system international (SI) units.

The following clinical laboratory analyses will be performed:

Table 6. Clinical Laboratory Test

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, phosphates, potassium, sodium, bilirubin (total, direct), total protein, uric acid, Troponin I, serum 25-OH vitamin D, thyroid stimulating hormone, intact parathyroid hormone and creatinine clearance, estimated*.
Hematology:	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential count, absolute neutrophil count, lymphocyte count, and platelet count, total neutrophils (%), lymphocytes (%), monocytes (%), monocytes (10^9/L)*, eosinophils (%), eosinophils(10^9/L)*, basophils (%), basophils (10^9/L)*, immature granulocytes (10^9/L)* and immature granulocytes/leukocytes (%)*.
Urinalysis:	Color, pH, specific gravity, glucose, ketones, leukocytes, nitrite, protein, bilirubin, urobilinogen, occult blood, and microscopic examination (only if urinalysis dipstick results are abnormal).

*= parameters analyzed only from the central laboratory not in [redacted] laboratory.

13.3. Vital Signs and Weight

Vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature) and weight will be measured at time points specified in the schedule of assessments (Appendix 16.1).

Descriptive statistics for actual values and changes from baseline of vital signs and weight will be summarized by treatment group, parameter and visit. For the baseline value of the vital signs, the vital signs results and hypersensitivity/allergic reaction monitoring results will be considered.

All vital signs and weight will be listed for each patient by treatment group and visit.

13.4. Electrocardiograms

12-lead ECGs will be performed at the time points specified in the schedule of assessments (Appendix 16.1).

Findings of 12-Lead ECG will be classified as either “Normal”, “Abnormal, Not Clinically Significant”, or “Abnormal, Clinically Significant”.

The number and percentage of patients will be summarized by treatment group and visit, in the form of a shift table to detect changes from baseline. All 12-lead ECGs findings will be listed by treatment group and visit.

13.5. Physical Examination

Physical examinations will be performed at the time points specified in the schedule of assessments (Appendix 16.1). The following body systems will be examined:

- General Appearance
- Head and Neck
- Oral
- Skin
- Cardiovascular System
- Respiratory System
- Abdominal System
- Neurological System
- Musculoskeletal System
- Lymph Nodes

Findings of physical examination will be collected as "Normal", "Abnormal, Not Clinically Significant" and "Abnormal, Clinically Significant". The number and percentage of patients will be summarized by treatment group, body system and visit in the form of a shift table to detect changes from baseline. All physical examination data will be listed by treatment group, visit and body system.

13.6. Local Site Pain

All patients will assess local site pain using 100 mm VAS immediately after the end of administration of study drug (not exceeding 15 minutes) at the time points specified in the schedule of assessments (Appendix 16.1).

Local site pain data will be summarized using descriptive statistics by treatment group and visit. All local site pain data will be listed by treatment group and visit.

13.7. Hypersensitivity/Allergic Reaction Monitoring

Hypersensitivity/allergic reaction monitoring will be assessed by vital sign monitoring (including systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature) within 15 minutes before the start of the study drug administration and 1 hour after injection (± 10 minutes) at each scheduled time points in the Appendix 16.1.

The number and percentage of patients who have clinically notable hypersensitivity result will be summarized by treatment group, visit, time points and parameter. The criteria for clinically notable results are defined as follows:

Table 7. Criteria for Clinically Notable Hypersensitivity Results

Parameter	Low	High
Systolic blood pressure (mmHg)	≤ 90	≥ 160
Diastolic blood pressure (mmHg)	≤ 50	≥ 90
Heart rate (beats per minute)	≤ 50	≥ 100
Respiratory rate (breaths per minute)	≤ 12	≥ 20
Body temperature (°C)	≤ 35.0	≥ 38.0

All hypersensitivity data via vital sign measurements will be listed for each patient by treatment group, visit and time points. High and low flags will also be presented in the listing to show whether a value is outside of the normal range.

13.8. Immunogenicity

Blood samples for immunogenicity assessments (central laboratory) will be collected at the time points specified in the schedule of assessments (Appendix 16.1). Additional immunogenicity will be assessed when immune-related AEs occur. For patients who early discontinue the study treatment, the samples will be collected until the next scheduled study drug administration visit. The samples collected after the next scheduled study drug administration visit will be flagged in the listing but excluded from the table.

Immunogenicity assessments consist of both anti-drug antibody (ADA) including ADA titer and neutralizing antibody (NAb) assays.

The ADA assay will follow a three-tiered approach consisting of screening assay, confirmatory assay and titration.

The test outcome for the screening assay will be reported as ‘Potential Positive’ or ‘Negative’. Samples that are ‘Potential Positive’ in the screening assay will be undergone further testing in the confirmatory assay to determine if the samples are a true positive. The test outcome for the confirmatory assay will be ‘Positive’, ‘Negative’ or ‘Not applicable (N/A)’. ‘Positive’ indicates a true positive test outcome, ‘Negative’ is considered negative, and ‘N/A’ indicates the test outcome was negative at the screening phase of the process. Patients with a ‘Negative’ test outcome for either screening or confirmatory assays will be considered negative for the overall ADA assessment. For further characterization, the antibody level will be assessed by titration in confirmed positive samples.

Samples that are positive in the ADA confirmatory assay will be analyzed further to conduct a NAb assessment. The test outcome for the screening assay will be ‘Positive’ or ‘Negative’.

The results of the final ADA and the screening NAb incidence will be summarized by treatment group and each scheduled visit. Also, the number of patients with at least one ADA/NAb positive result after the first study drug administration of each treatment period including scheduled and unscheduled visits (Treatment Period I: Week 0 / Treatment Period II: Week 52) regardless of their ADA status at baseline will be presented.

The results of scheduled visits for ADA/NAb will be classified as Treatment Period I or II by Week 52 (Treatment Period I for the data up to Week 52, otherwise Treatment Period II). On the other hand, the results of unscheduled visits for ADA/NAb will be classified as Treatment Period I and II by the following rules:

- Treatment Period I: ADA/NAb results with an assessment date on or before the date of study drug administration in Treatment Period II, or the results for patients who did not enter Treatment Period II will be included.

- Treatment Period II: ADA/NAb results with an assessment date after the date of study drug administration in Treatment Period II will be included.

The ADA titer will be summarized by treatment group and each scheduled visit using descriptive statistics.

A listing showing immunogenicity test results for each patient will be provided by treatment group and visit.

14. CHANGES FROM PROTOCOL

- The definition of PK/PD set was changed so that only patients with post-treatment result up to Treatment Period I could be included in the PK/PD set.
- In the definition of the PK/PD – Treatment Period II Subset, since the blood sampling test at Week 52 was performed before the study drug administration, the analysis subset was changed to include only the results after Week 52, not the results collected at or after Week 52.
- Subgroup analysis by race for primary efficacy endpoint was deleted as all patients were White.

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16. APPENDIX

16.1. Schedule of Assessments

	Screening	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	X[5]														
Randomization[6]		X										X				
Efficacy assessment – Predose, if study drug is 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 is 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 is administered on the same visit																
Immunogenicity Sampling[15]		X			X	X	X	X	X		X	X		X	X	X

	Screening	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**				
Pharmacokinetic Sampling[16]		X	X	X	X	X	X	X	X		X	X		X	X	X
Pharmacodynamic 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														

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; 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; NYHA, New York Heart Association; OPAQ-SV, osteoporosis assessment questionnaire-short version; RNA, ribonucleic acid; QoL, quality of life; VAS, visual analog scale.

Note: For patients who early discontinue study treatment or initiated different osteoporosis medication (including those prohibited by the protocol), every effort should be made to complete regularly scheduled study visits, and PK, PD, and immunogenicity samples will be collected until the next study drug administration scheduled visit. When a patient discontinues study treatment after administration of the study drug at Week 52, the PK, PD, and immunogenicity samples will be collected until Week 78 visit. Especially, if a patient discontinues the study treatment prior to Week 52, the patient should return to the study center at Week 52 for the primary efficacy assessment. If a patient cannot or is unwilling to attend any visit(s), a safety follow-up (e.g., adverse events, concomitant medications) will be conducted by telephone according to the study visit schedule.

1. An EOS visit will occur at the Week 78 visit for all patients who completed or discontinued study treatment.
2. A dosing visit window of ± 3 days is allowed for Week 26 visit and that of ± 5 days is allowed for Week 52 visit. If any study visit has to be rescheduled, subsequent visits should follo w the original visit date scheduled.
3. At Screening, hepatitis B will be assessed in all patients. A patient with past hepatitis B virus is allowed if resolved. If the patient develops hepatitis B reactivation, the study drug must be stopped. Further eligibility for hepatitis B infection will be confirmed according to the Table 6-1 in the protocol. At Screening, hepatitis C antibody will be assessed in all patients. If hepatitis C antibody test result is positive, a HCV RNA test will be performed at Screening. If the HCV RNA test result is positive, the patient will be excluded from the study; If the H CV RNA test result is negative, the patient can be included in the study at the Investigator's discretion. Further evaluation for the patients who are enrolled based on HCV RNA test can be done depending on the Investigator's discretion during the study. HIV test will be assessed in all patients at Screening. If the HIV test result is positive, the patient will be excluded f rom the study. Hepatitis B, hepatitis C, and HIV analysis will be performed at the central laboratory.
4. At Screening, patients who have history of heart failure will be assessed for the presence of congestive heart failure according to the NYHA functional classification.
5. The inclusion and exclusion criteria need to be confirmed by screening results prior to the randomization on Day 1.

6. Patients will be randomly assigned to one of two treatment groups (either CT-P41 or US-licensed Prolia) on Day 1 prior to the study drug administration. Second randomization will be performed prior to the study drug administration on Week 52. Patients who are initially randomized to CT-P41 in Treatment Period I will continue to receive CT-P41. Patients who are initially randomized to US-licensed Prolia in Treatment Period I, will be re-randomized in a ratio of 1:1 to switching arm (CT-P41) or non-switching arm (US-licensed Prolia).
7. Bone mineral density will 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 will be performed a t a central imaging vendor. If needed, Week 26 DXA scan can be occurred at a separate site visit within ± 3 days visit window of Week 26 visit, which is followed by the study drug ad ministration occurring within the same visit window of Week 26 visit. At Week 52 visit, the DXA scan will be analyzed by both the central imaging vendor and the study center. If nee ded, Week 52 DXA scan can be occurred at a separate site visit within ± 5 days visit window of Week 52 visit, which is followed by the study drug administration occurring within the same visit window of Week 52 visit. A BMD assessor for the local reading will be assigned to each study center. If possible, it is recommended that the local reading will be performed by the same person at each study center throughout the study period. The local reading result at Week 52 will be used for the stratification factor of the second randomization.
8. Lateral spine X-ray will 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 need ed, the lateral spine X-ray at Week 26 or Week 52 can be occurred at a separate site visit within ± 3 days or ± 5 days visit window of Week 26 or Week 52 visit respectively, which is f ollowed 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) will be measured after 5 minutes of rest (sitting).
10. All scheduled 12-lead ECG will be performed at the study center after the patients have 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 can be conducted at the Investigator's discretion.
11. Physical examination including oral examination (including mouth, gums, teeth, tongue).
12. Urinalysis analysis will be performed at the central laboratory.

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

13. Hematology, clinical chemistry, and other test samples will be 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 should be closely conducted and adequately treated at the Investigator's discretion, if occurr ed.

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 (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), 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 will be obtained to determine the study drug administra tion at Weeks 26 and 52. The clinical laboratory tests will be monitored for hypocalcaemia and will be analyzed at the local laboratory. If abnormal results are reported, patients will be treated accordingly and follow-up actions will be taken at the Investigator's discretion. If needed, the tests can 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 is followed by the study drug administration occurring within the same visit window of each visit. Albumin-adjusted to tal serum calcium level will be 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 is 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 will be collected prior to dosing of the study drug if study drug is administered on the same visit. Other samples could be taken at any time of the s cheduled visit. Additional immunogenicity will be assessed when immune-related AEs occur. Analysis will be performed at the central laboratory. For patients who early discontinue st udy treatment, immunogenicity samples will be collected until the next study drug administration scheduled visit and further immunogenicity sampling is unnecessary. When a patient

discontinues study treatment after administration of the study drug at Week 52, the immunogenicity samples will be collected until Week 78 visit.

16. Samples for pharmacokinetic testing should be collected up to 30 minutes prior to dosing of the study drug if study drug is administered on the same visit. Other samples could be taken at any time of the scheduled visit. Analysis will be performed at the central laboratory. For patients who early discontinue study treatment, pharmacokinetic samples will be collected until the next scheduled study drug administration visit and further pharmacokinetic sampling is unnecessary. When a patient discontinues study treatment after administration of the study drug at Week 52, pharmacokinetic samples will be collected until Week 78 visit.
17. Samples for pharmacodynamic testing should be taken in the morning after fasting overnight for 8 hours prior to assessment, and the patients have to refrain from intense exercise the day prior to PD assessment. Analysis will be performed at the central laboratory. For patients who early discontinue study treatment, pharmacodynamic samples will be collected until the next study drug administration scheduled visit and further pharmacodynamic sampling is unnecessary. When a patient discontinues study treatment after administration of the study drug at Week 52, pharmacodynamic samples will 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) will be assessed to monitor for possible hypersensitivity reactions. In addition, hypersensitivity will be 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 must be available and any types of ECG can be performed. For patients who early discontinue study treatment, monitoring of hypersensitivity/allergic reactions is unnecessary after the discontinuation.
19. Injection site reaction will be assessed 30 minutes (± 10 minutes) after the end of administration of the study drug. For patients who early discontinue study treatment, assessment of injection site reaction is unnecessary after the discontinuation.
20. Patients will assess 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 discontinue study treatment, assessment of local site pain is unnecessary after the discontinuation.
21. All patients will also receive 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 will be collected via patient's diary and will be also recorded in both the source documents and eCRF.
22. Radiography will be performed as required for confirmation of suspected fractures. Radiography will be 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 will be recorded. Use of all prior and concomitant medications for the treatment of osteoporosis, from the diagnosis of disease until the EOS visit, will be recorded. For eligibility check, relevant medication history will be also recorded.
24. Adverse events will be assessed from the signed date of ICF until EOS visit, regardless of the relationship to the study drug. The condition of the patient will be monitored throughout the study for any signs or symptoms. After the last EOS visit, serious adverse drug reactions will be reported to CELLTRION, Inc. or its designee.

16.2. Table of CTCAE Terms and Grades

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransferase increased	Alanine Aminotransferase (ALT)	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase increased	Alkaline phosphatase (ALP)	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL; <LLN - 100 g/L; <LLN – 6.2 mmol/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 – 80 g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	-
Aspartate aminotransferase increased	Aspartate Aminotransferase (AST)	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Blood bicarbonate decreased	Bicarbonate	Low	<LLN	-	-	-
Blood bilirubin increased	Total Bilirubin	High	>ULN - 1.5 x ULN if baseline was normal; > 1.0	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0	>3.0 - 10.0 x ULN if baseline was normal; >3.0	>10.0 x ULN if baseline was normal; >10.0 x

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
			- 1.5 x baseline if baseline was abnormal	x baseline if baseline was abnormal	- 10.0 x baseline if baseline was abnormal	baseline if baseline was abnormal
Blood lactate dehydrogenase increased	Lactate Dehydrogenase (LDH)	High	>ULN	-	-	-
Cholesterol high	Total Cholesterol	High	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
CPK increased	Creatine Phosphokinase (CPK)	High	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Creatinine increased [1)]	Creatinine	High	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Eosinophilia	Eosinophil Count	High	>ULN and >Baseline	-	-	-
GGT increased	Gamma Glutamyl Transferase (GGT)	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Hemoglobin increased	Hemoglobin	High	Increase in >0 - 2 g/dL from ULN	Increase in >2 - 4 g/dL from ULN	Increase in >4 g/dL from ULN	-
Hypercalcemia	Calcium	High	Corrected serum calcium of >ULN - 11.5 mg/dL;	Corrected serum calcium of >11.5	Corrected serum calcium of >12.5	Corrected serum calcium of >13.5

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
			>ULN - 2.9 mmol/L	- 12.5 mg/dL; >2.9 - 3.1 mmol/L	- 13.5 mg/dL; >3.1 - 3.4 mmol/L	mg/dL; >3.4 mmol/L
Hyperkalemia	Potassium	High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypermagnesemia	Magnesium	High	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L;
Hypernatremia	Sodium	High	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L;	>160 mmol/L
Hypertriglyceridemia	Triglyceride	High	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L
Hyperuricemia	Uric Acid	High	>ULN	-	-	-
Hypoalbuminemia	Albumin	Low	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL;<30 - 20 g/L	<2 g/dL;<20 g/L	-
Hypocalcemia	Calcium	Low	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L
Hypoglycemia	Glucose	Low	<LLN-55mg/dL;<LLN-3.0 mmol / L	< 55 -40mg/dL;< 3.0 – 2.2 mmol / L	< 40 -30mg/dL;< -2.2 – 1.7 mmol / L	<30mg/dL; <1.7mmol/L
Hypokalemia	Potassium	Low	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L	<2.5 mmol/L

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Hypomagnesemia	Magnesium	Low	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L;
Hyponatremia	Sodium	Low	<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L regardless of symptoms	<120 mmol/L
Leukocytosis	White Blood Cells	High	-	-	>100,000/mm^3	-
Lymphocyte count decreased	white blood cell count with differential count	Low	<LLN - 800/mm^3; <LLN – 0.8 x $10e^9$ /L	<800 - 500/mm^3; <0.8 – 0.5 x $10e^9$ /L	<500 - 200/mm^3; <0.5 – 0.2 x $10e^9$ /L	<200/mm^3; <0.2 x $10e^9$ /L
Lymphocyte count increased	white blood cell count with differential count	High	-	>4000/mm^3 - 20000/mm^3	>20000/mm^3	-
Neutrophil count decreased	Absolute Neutrophil Count	Low	<LLN - 1500/mm^3; <LLN - 1.5 x $10e^9$ /L	<1500 - 1000/mm^3; <1.5 - 1.0 x $10e^9$ /L	<1000 - 500/mm^3; <1.0 - 0.5 x $10e^9$ /L	<500/mm^3; <0.5 x $10e^9$/L
Platelet count decreased	Platelet count	Low	<LLN - 75,000/mm^3;<LLN - 75.0 x $10e^9$ /L	<75,000 - 50,000/mm^3;<75.0 - 50.0 x $10e^9$ /L	<50,000 - 25,000/mm^3;<50.0 - 25.0 x $10e^9$ /L	<25,000/mm3; <25.0 x $10e^9$ /L
White blood cells decreased	White blood cells	Low	<LLN - 3000/mm^3; <LLN – 3.0 x $10e^9$ /L	<3000 - 2000/mm^3; <3.0 - 2.0 x $10e^9$ /L	<2000 - 1000/mm^3; <2.0 - 1.0 x $10e^9$ /L	<1000/mm^3; <1.0 x $10e^9$/L

LLN = lower limit of normal, ULN = upper limit of normal.
1) The most severe grade is counted if the CTCAE grade is discrepant by multiple definitions.
Note: The LLN and ULN values will be the lower and upper limits of the normal ranges as provided by laboratories.